FINAL DRAFT
ECAO-CIN-025
March, 1985
EPA-600/X-84-178-1

United States
Environmental Protection
Agency

EPA

Research and Development

PB86-117827

DRINKING WATER CRITERIA DOCUMENT FOR MERCURY

Prepared for

OFFICE OF DRINKING WATER

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SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

2.

3. RECIPIENT'S ACCESSION NO. PB86 117827/AS

SUBTITLE Drinking Water Criteria Document for Mercury

5. REPORT DATE 3/85

6. PERFORMING ORGANIZATION CODE

HOR(S) Environmental Protection Agency

8. PERFORMING ORGANIZATION REPORT NO.

PERFORMING ORGANIZATION NAME AND ADDRESS

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS

U.S. Environmental Protection Agency
Office of Drinking Water (WH-550)
401 M St., S.W., Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED Scientific review

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on mercury. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of mercury
- Toxicokinetics and human exposure to mercury
- Health Effects of mercury in humans and animals
- Mechanisms of toxicity of mercury
- Quantification of toxicological effects of mercury

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Mercury properties Mercury exposure Mercury toxicity Drinking Water		

18. DISTRIBUTION STATEMENT OPEN

19. SECURITY CLASS (This Report) Non-sensitive

21. NO. OF PAGES 140

20. SECURITY CLASS (This page) Non-sensitive

22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ACh	Acetylcholine
ADI	Acceptable daily intake
bw	Body weight
CNS	Central nervous system
GI	Gastrointestinal
HA	Health advisory
IgG	Immunogamma globulin
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Dose lethal to 50% of the population
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
s.c.	Subcutaneous
WHO	World Health Organization
ww	Wet weight

I. SUMMARY

Mercury is a silver-white metal that is liquid at room temperature. It exists in three oxidation states: elemental (Hg^0), mercurous ($Hg_2{}^{++}$) and mercuric (Hg^{++}) and in several chemical forms (e.g., methyl mercury, mercuric mercury and mercury vapor). Mercury reacts to form both inorganic and organic compounds. The concentration of mercury in natural waters is quite low. The mercury content of lakes and reservoirs ranges from <0.1-1.8 µg/ℓ and, with few exceptions, groundwater samples are below the detection limit of 0.1 µg/ℓ. Examination of 273 community recreation and Federal installation water supplies indicated that either no detectable mercury was present or the concentrations were <1 µg/ℓ in 95.5% of the samples. The predominant form of mercury present in uncontaminated water is thought to be inorganic having an oxidation state of +2. This inorganic mercury is in part ionic [$Hg^{2}+$] and in part the neutral aquatic complex $Hg(OH)_2^0$.

The primary route of exposure to mercury is through the diet. Exposure to mercury may also occur by inhalation of mercury vapor. Mercury vapor concentrations may range from 3-4 ng Hg/m³ in rural areas to 10 ng Hg/m³ in urban areas. Further details on the health effects of inhaled mercury are given in the Mercury Health Effects Update: Final Report (U.S. EPA, 1984).

Mercury is absorbed after oral dosing and distributed systemically to all organs with the greatest amounts accumulating in the kidneys. The absorption of most organic mercury compounds is quite high as compared with inorganic salts, which generally have an absorption coefficient of 10% or less in adults. The primary route of excretion for short-chain alkyl mercurials is by the fecal route; with inorganic mercury and organic compounds, which have larger side-chains, the fecal and urinary routes are about equally important. For most mercury compounds the elimination half-times ranged from 45-50 days.

The primary effects of exposure to short-chain alkyl mercurials include both central and peripheral nervous system pathology leading to a variety of behavioral and neurophysiological effects. Following intake of inorganic salts, the kidney is the primary target organ. This is also true for many of the larger organic molecules since they break down rapidly to release ionic mercury. Exposure of large numbers of victims to methyl and ethyl mercury at toxic levels (in excess of 300 μg/day) for relatively long periods has occurred because of the presence of a silent period during which no symptoms are noted for up to 6 months and even longer from the start of exposure.

Unborn children and infants are more susceptible to the toxic effects of mercury than adults. Mental retardation was found in a group of children with mothers having hair mercury concentrations in the range of 18-67 ppm (Marsh et al., 1981). When estimated blood mercury levels of the mothers during pregnancy were ~60-200 μg/ℓ there was no indication of mental retardation. Permanent damage often occurs as a result of an inhibition of nervous system development. Structural abnormalities have also been shown to occur in animal experiments but at concentrations well above those causing brain damage.

Toxic manifestations have usually been ascribed to the ability of mercury to penetrate cell membranes and react with sulfhydryl groups of proteins. This leads to enzyme inhibition as well as a disruption of other cellular processes. Toxic responses in humans can generally be detected at blood levels >300 µg/ℓ. For methyl mercury this requires a daily intake of 3-7 µg or more. At lower intake levels symptoms may not be detected for up to several months.

Little evidence exists concerning the mutagenic effects of mercury. Mercury has not been shown to be carcinogenic in epidemiological studies but was reported to cause renal tumors in rats.

A World Health Organization (WHO) Expert Group has recommended an international standard of 1 µg/ℓ for drinking water. The U.S. EPA has recommended a standard of 2 µg/ℓ for drinking water (144 ng/ℓ for the protection of ambient water quality) (U.S. EPA, 1973, 1980).

A subchronic study using a sensitive immuno-pathologic endpoint, following exposure to mercuric chloride, was selected to derive the recommended ADI. In this study the NOAEL was determined to be 15.8 µg Hg/kg bw/day. The ADI for a 70 kg man was then estimated as 11 µg/day. Based on intake of 2 ℓ of water/day an AADI of 5.5 µg Hg/ℓ is recommended. This AADI is for inorganic mercury in the drinking water only.

II. GENERAL INFORMATION AND PROPERTIES

Mercury is a silver-white metal with an atomic weight of 200.59. A liquid at room temperature, its melting point is -38.87°C and its boiling point ranges from 356-358°C. It can exist in three oxidation states: elemental, mercurous and mercuric; it can be part of both inorganic and organic compounds. The metal is insoluble and is not attacked by water. At 20°C, the specific gravity is 13.546 and the vapor pressure is 0.0012 mm Hg (Stecher, 1968).

Mercury exists in a number of forms in the environment. The more commonly found mercuric salts (with their solubilities in water) are as follows: mercuric chloride ($HgCl_2$) (1.0 g/13.5 mℓ water), mercuric nitrate $[Hg_2(NO_3)_2]$ (soluble in a "small amount" of water) and $[Hg_2(CH_3COO)_2]$ (1.0 g/2.5 mℓ water). Mercurous salts are much less soluble in water. Mercuric nitrate $Hg_2(NO_3)$ will solubilize only in 13 parts water containing 1% HNO_3. Hg_2Cl_2 is practically insoluble in water. Because of this, mercurous salts are much less toxic than the mercuric forms (Stecher, 1968).

A major use of mercury has been as a cathode in the electrolytic preparation of chlorine and caustic soda; this accounted for 33% of total demand in the United States in 1968. Electrical apparatus (lamps, arc rectifiers and mercury battery cells) accounted for 27%, industrial and control instruments (switches, thermometers and barometers) and general laboratory applications accounted for 14% of demand. Use of mercury in antifouling and mildew proofing paints (12%) and mercury formulations used to control fungal diseases of seeds, bulbs, plants and vegetation (5%) were other major utilizations; however, mercury is no longer registered by the EPA for use in paints or fungicides. The remaining 9% was used for dental amalgams, catalysts, pulp and paper manufacture, pharmaceuticals, metallurgy and mining.

It is customary (Maximum Allowable Concentrations Committee, 1969) to consider three broad categories of the physical and chemical forms of mercury. These categories are selected mainly because of the difference in their toxic properties and in the hazards they present to human health. The first category consists of metallic mercury. Mercury in the zero oxidation state (Hg^0) is usually referred to as mercury vapor when present in the atmosphere or as metallic mercury when present in its liquid form. The second category comprises the inorganic compounds of mercury, which includes the salts of the two oxidation states of mercury, Hg_2^{++} (mercurous salts) and Hg^{++} (mercuric salts). The third major category contains the so-called organic mercurials or organic mercury compounds. These are defined as those compounds in which mercury is attached to at least one carbon atom by a covalent bond. The toxic properties in this third category, however, vary enormously. The most important subgroup in the organo-mercurials category is comprised of the methyl mercury and related short-chain alkyl mercurial compounds. From the point of view of environmental exposures, the methyl mercury compounds are the ones of greatest concern. The other organo-mercurials may take the form of aryl and alkoxyaryl mercurials as well as a wide variety of other organo-mercurials used in medicine and agriculture. In general these organic forms of mercury are much less toxic than the short-chain alkyl mercurials.

III. TOXICOKINETICS

The disposition of mercury in the body has been reviewed by a Task Group on Metal Accumulation (1973), by a WHO Expert Committee (WHO, 1976) and most recently by the U.S. EPA (1980, 1984). Coverage will emphasize inorganic salts, as well as organic mercury compounds, with the exception of mercury diuretics which are virtually obsolete for therapeutic use. Inhalation of mercury vapor is described in more detail in the Mercury Health Effects Update (U.S. EPA, 1984).

Absorption

Inorganic Mercury. Rahola et al. (1971) reported findings on gastrointestinal absorption of inorganic mercury given to 10 volunteers (see also the Elimination Section). Five males and three females received a single tracer dose of radioactively labeled mercuric nitrate bound to calf liver protein containing ~6 μg Hg/dose. Two other volunteers received an acid solution of mercuric nitrate. During the 4-5 days following both treatments, an average of 85% of the dose was eliminated in the feces, while urinary excretion averaged only 0.17%. The average absorption was estimated to equal about 7% and did not differ between the bound and unbound forms. However, this study does not differentiate between Hg^{++} that was never absorbed versus that which was absorbed and then excreted in the bile.

Clarkson (1971) also reported that absorption of mercuric chloride was poor in mice averaging only 1-2%. Kostial et al. (1978), however, reported a strong influence of age and diet. Their studies showed that absorption of mercuric chloride (Hg^{++}) averaged 38% in 1-week-old suckling mice compared with 7% in adults on a milk diet and 1% in adults fed a standard diet.

Methyl Mercury. Several quantitative measurements have been made on the absorption of methyl mercury compounds in the GI tract. In a study by Aberg et al. (1969) male volunteers received a single oral tracer dose of 11 µg methyl mercuric nitrate ($CH_3{}^{203}HgNO_3$) in aqueous solution. Daily measurements of whole body retention of mercury along with excretion in the feces and urine indicated that absorption was virtually complete. Miettinen (1973) reported similar results for methyl mercury bound to protein. The findings of the tracer studies have been confirmed in observations of volunteers who ingested tuna fish contaminated with mercury (Turner et al., 1974, 1975). In studies of the dietary intake of methyl mercury in homemade bread contaminated with a fungicide, Al-Shahristani et al. (1976) obtained results consistent with a high degree of absorption from the diet.

Ethyl, Aryl and Alkoxyalkyl Mercurials. Little quantitative information is available for other organic mercurials found in the environment. Ethyl mercury is evidently well absorbed, however, since episodes of accidental poisoning related to ingestion of food contaminated with this compound have been reported (Jalili and Abbasi, 1961). Phenyl mercury salts added and allowed to combine with animal foodstuffs underwent virtually complete absorption in mice (Clarkson, 1972b). In long-term studies with rats, Fitzhugh et al. (1950) also showed that phenyl mercury salts were much more efficiently absorbed than inorganic mercury.

Metallic Mercury. Liquid mercury has long been considered to be poorly absorbed from the GI tract. Based on the data of Bornmann et al. (1970) in animals given gram quantities by mouth, Friberg and Nordberg (1973) calculated that <0.01% of an administered dose of metallic mercury was absorbed. There have been reports that blood levels of mercury were increased in people who accidently ingested several grams of metallic mercury (Suzuki and Tanaka, 1971).

Distribution and Metabolism

Mercuric Salts. Nearly all mercury entering the body becomes bound to thiol groups in proteins and other biological molecules (Clarkson, 1972b). The equilibrium constant between the sulfur atom of a thiol group and mercury is many orders of magnitude greater than for reversible binding between mercury and other types of ligands (Hughes, 1957).

Renal cortical tissue has a remarkable ability to accumulate mercury, especially inorganic mercury compounds. Data published by Swensson and Ulfvarson (1968) indicated that kidney concentrations were 300 times that of blood levels following a single dose of mercuric nitrate. Rothstein and Hayes (1960) reported that the kidneys contained over 85% of the body burden of mercury 15 days or more after a single injection of mercury chloride in rats.

Inorganic salts of mercury, when given to rats, induced the synthesis of metallothionein in kidney tissue (Piotrowski et al., 1974). Exposure of rats to mercury vapor also results in the renal synthesis of metallothionein (Cherian and Clarkson, 1976). Since repeated daily doses of Hg^{++} result in tolerance to increased concentrations of mercury as well as metallothionein synthesis (Clarkson, 1977), and since this protein avidly binds mercury, it may play a protective role.

Webb and Magos (1976), however, have shown that protection against mercury nephrotoxicity by pretreatment with cadmium cannot be explained by pre-induced cadmium-thionein alone. Magos (1982) reported further that tolerance can be induced by nephrotoxic agents that do not induce thionein, and it is not conditional on a decrease in kidney content of mercury. Thus, while metallothionein is considered to play a role in the tolerance of the kidney to mercury, other factors are also important.

As a result of kidney accumulation, inorganic mercury is distributed in a very nonuniform manner. Only about 0.2-0.4% of the mercury was present in the blood, with a red cell to plasma ratio of about 0.4 in humans, 1 day after a tracer dose of Hg^{++} (4-14 μCi and 6 μg/subject) (Rahola et al., 1971). Mercuric mercury is generally transported in the bloodstream in equal proportions between plasma and red blood cells (Berlin, 1983). Unlike organic mercury compounds or inhaled mercury vapor, relatively small amounts penetrate the brain following exposure to inorganic mercury compounds (Jugo, 1976). According to Nordberg and Serenius (1969), brain levels of mercury following exposure to mercury vapor were 10 times higher than after an equal dose of an inorganic mercury compound.

Methyl Mercury and Other Short-Chain Alkyl Mercurials. Details on the distribution and retention of methyl mercury in man and animals were reviewed by Nordberg and Skerfving (1972), Clarkson (1972b), Task Group on Metal Accumulation (1973), WHO (1976) and by U.S. EPA (1980, 1984). Generally, methyl mercury compounds distribute readily to all tissues in the body after absorption from the GI tract. Unlike inorganic mercury, large concentration differences in various tissues are not seen because methyl mercury has the ability to cross diffusion barriers and penetrate all membranes without difficulty.

Based on observations in animals, distribution of methyl mercury within the body is fairly rapid with the exception of the brain. After injection of a single dose of ^{203}Hg labeled methyl mercury (0.0037 µCi/µg subcutaneously at a dose of 15 µg/g bw), maximum concentrations in the brain were reached within 2 days in the mouse (Mehra and Choi, 1981), within 3-4 days in the pig (Gyrd-Hansen, 1981) and within 4-10 days in the rat (Norseth and Clarkson, 1970).

Tracer studies in volunteers have revealed that ~5% of the ingested dose is deposited in the blood compartment after tissue distribution is completed. About 90% or more of the methyl mercury in the blood is associated with the red blood cells, resulting in a red-cell-to-plasma ratio as high as 20:1 (Bakir et al., 1973; Lundgren et al., 1967). Whole blood concentrations of mercury several times greater than the plasma concentrations were also reported for rabbits (Berlin, 1963), rats (Norseth and Clarkson, 1970) and pigs (Gyrd-Hansen, 1981).

According to observations of volunteers, the amount transferred to the head region following ingestion of a single dose of radioactive tracer is ~10% of the body burden after tissue distribution is complete (Aberg et al., 1969). From a review of Aberg's data as well as autopsy data, the Swedish Expert Group (1971) concluded that the brain-to-blood ratio was in the range of ~5:1. Nonhuman primates have a similar brain-to-blood ratio (Evans et al., 1977) while in pigs it averaged between 3:1 and 4:1 (Gyrd-Hansen, 1981). Cats, mice and most other mammals, on the other hand, have brain-to-blood ratios near unity. The rat has the lowest of all ratios, ~1:10 because of the high concentration of mercury in rat red blood cells (Task Group on Metal Accumulation, 1973; Clarkson, 1972b).

The concentration of methyl mercury in other tissues such as muscle, liver and kidney usually does not vary by more than a factor of 2 or 3; the highest levels are usually found in the kidney cortex. In muscle, the mercury is usually almost entirely in the form of methyl mercury, but in the kidney and liver a substantial proportion can be present as inorganic mercury. Mehra and Choi (1981), for example, reported that 21 days after a single dose of methyl mercury chloride in mice, 27% of the mercury content of the liver and 37% in the kidney was in the inorganic form. Autopsy data in Iraq also indicate a substantial proportion present as inorganic mercury in the liver (Magos et al., 1976). The fraction of inorganic mercury in brain is low (~4% of total mercury) and does not appear to increase with time (Norseth and Clarkson, 1971).

Methyl mercury is readily transferred from mother to fetus across the placenta. At birth the concentration in the umbilical cord or infant blood is usually slightly higher than that observed in maternal blood. In observations of women having normal pregnancies and on a low to moderate fish intake, Tejning (1970) reported that methyl mercury in the fetal blood cells was about 30% higher than in the maternal cells. Suzuki et al. (1971) and Kuhnert et al. (1981) confirmed the finding of higher fetal blood concentrations. The studies on the outbreak of methyl mercury poisoning in Iraq (Bakir et al., 1973; Amin-Zaki et al., 1974a, 1976) also showed that methyl mercury was readily transferred across the placenta, resulting in higher concentrations in fetal when compared with maternal blood at the time of delivery. This difference is most likely due to the concentration of mercury in the red blood cells rather than the plasma. The greater infant blood level is not accounted for by a higher hematocrit in the infant (Bakir et al., 1980).

Methyl mercury is secreted in mother's milk. The studies of the Iraqi outbreak revealed the close correlation between maternal milk and blood concentrations; the milk mercury concentration was normally ~5% of the blood concentration (Bakir et al., 1973). About 40% of the mercury in milk was found to be in the inorganic form. Skerfving et al. (1974), in a study of 15 lactating females following intake of methyl mercury from fish, also noted a correlation with blood concentrations but found a smaller percentage (~20%) of mercury in the form of methyl mercury in the milk.

Mercury is accumulated in head hair after exposure to methyl mercury compounds. A variety of observations (Table III-1) indicate that the hair-to-blood concentration ratio is about 250:1. Mercury is accumulated in the hair at the time of its formation and thus, in freshly formed hair, the concentration is proportional to that in blood. Once incorporated into the hair sample, the concentration of mercury is stable; so, as the hair is examined longitudinally, a history is obtained of previous blood concentrations (Clarkson et al., 1976). Hair grows at ~1 cm per month (Al-Shahristani and Shihab, 1974) so that the measurement of each 1 cm segment corresponds to the average blood concentration during a particular month.

TABLE III-1

Relationship Between Concentrations of Mercury in Samples of Blood and Hair in People Having Long-term Exposure to Methyl mercury from Fish*

No. of Subjects	Whole Blood (x) (mg/kg) Range	Hair (y) (mg/kg) Range	Linear Regression
12	0.004 - 0.65	1 - 180	$y = 280x - 1.3$
51	0.004 - 0.11	1 - 30	$y = 230x + 0.6$
50	0.005 - 0.27	1 - 56	$y = 140x + 1.5$
45	0.002 - 0.80	20 - 325	$y = 260x + 0$
60	0.044 - 5.5	1 - 142	$y = 230x - 3.6$

*Source: WHO, 1976

Although not every hair grows at a constant rate, it is still a very useful medium to recapitulate past exposures as well as to give information on current exposure to methyl mercury. An example of the close parallel between concentration in hair and blood is shown in Figure III-1 (Amin-Zaki et al., 1976). Phelps et al. (1980) measured blood and hair mercury levels in 339 subjects exposed to methyl mercury from ingestion of contaminated fish and observed a linear regression $y = 296x - 0.47$ ($r=0.935$) for the relationship between the concentration of mercury in samples of blood and hair (y = mg Hg/kg hair and x = mg Hg/kg whole blood). Inorganic and organic mercury levels were measured; the ratio of inorganic to organic mercury in hair was 0.213. It was found that neither the concentration nor the form of mercury changed once it was deposited in the hair; longitudinal analysis showed that the ratio of inorganic to organic mercury was constant.

Aryl and Alkoxyalkyl Mercurials. Unlike short-chain organic mercury compounds, the aryl and alkoxyalkyl compounds show a highly uneven distribution pattern similar to that of inorganic mercury salts (Swensson and Ulfvarson, 1968). The kidney is the main organ of accumulation after conversion to inorganic mercury in all cases. Prior to the conversion, the liver is the main organ of accumulation. This distribution is likely due to the rapid cleavage of the carbon mercury bond (Clarkson, 1972b).

Elimination

Salts of Inorganic Mercury. Studies by Rahola et al. (1971) of volunteers who ingested tracer doses of inorganic mercury for 45 days revealed that urine and fecal excretion were approximately equal after the unabsorbed oral dose was cleared by the GI tract (see also the Absorption Section). It

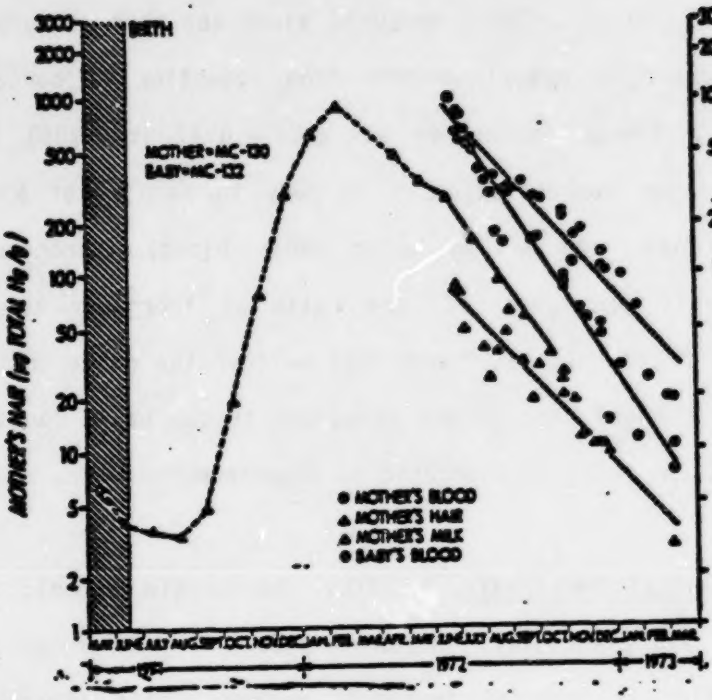

FIGURE III-1

Concentration of total mercury in 1 cm segments of sample of mother's hair, whole blood and milk, and baby's blood (postnatal exposure). Concentrations in milk and blood are plotted according to dates of collection.

Source: Amin-Zaki et al., 1976

is possible that urinary excretion could be increased by kidney damage. For example, Cember (1962) reported that cytotoxic doses of inorganic mercury could lead to desquamation of renal tubular cells, resulting in a sharp increase in mercury excretion. Magos (1973) reviewed other studies where agents producing kidney damage, leading to desquamation of cells, caused an increase in urinary mercury excretion. In the tracer study by Rahola et al. (1971), the whole-body half-time equaled 45 days. This was consistent with an excretion in urine and feces amounting to a total of 1.5% of the remaining body burden per day. Miettinen (1973) reported a biological half-time of inorganic mercury in the whole-body of 37 days in five female volunteers and 48 days in the same number of male volunteers. The elimination rate after 45 days of exposure was the same whether the mercury was administered as a proteinate or in an ionic form.

Methyl Mercury and Other Short-Chain Alkyl Mercurials. The elimination of mercury from the body in humans exposed to methyl mercury occurs predominantly by the fecal route. Less than 2% of excretion occurs in the urine. The form of mercury in feces is almost completely the inorganic (Turner et al., 1974); about 90% of the mercury in urine is inorganic (Bakir et al., 1973). These observations indicate that an important step in the excretion process is the cleavage of the carbon-mercury bond. The site of cleavage in the body is not known. Animal experiments indicate that there is a substantial biliary excretion of methyl mercury which will likely be reabsorbed to a large extent by the intestines (Norseth and Clarkson, 1971).

There is a possibility that some transformation of methyl mercury from biliary excretion to the inorganic form may occur in the gut. Rowland et al. (1980), for example, showed that treatment of rats with antibiotics to eliminate intestinal microflora increases the tissue concentration and toxic effects of ingested methyl mercury chloride. This protective effect of intestinal bacteria was shown to be due to transformation of some of the methyl mercury present to metallic mercury and a sulfide.

The rate of decline in blood concentration of methyl mercury after cessation of exposure is described well by a single biological half-time as evidenced by both tracer experiments in volunteers and also in people ingesting substantial amounts of methyl mercury from either fish or contaminated food (Table III-2). The tracer experiments reveal a half-time of at least 50 days. The range of half-times reported in both tracer experiments and in people having substantial exposures is large. Whether this range of values is due to individual differences or to experimental or observational inaccuracies in the measurements is not clear.

The study by Al-Shahristani and Shihab (1974) indicated a bimodal distribution in 48 subjects. One group, accounting for 89% of the samples, had a mean half-time value of 65 days, while the other group had a mean value of 119 days.

Kershaw et al. (1980) studied the toxicokinetics of methyl mercury in six volunteers given a single meal of fish taken from a contaminated area of a river in northwestern Ontario. The fish contained 6-9.7 mg Hg/kg and the

TABLE III-2

Mercury Intake and Biological Half-times[a]

No. of Subjects	Hg Intake (µg/kg/day)	Half-times (days)			Reference
		Body	Blood	Hair	
5	trace	70[b]	--	--	Aberg et al., 1969
15	trace	76 (52-93)[c]	50	--	Miettinen, 1973
5	up to 5	--	--	(33-120)	Birke et al., 1967
5	up to 5	--	-- (58-164)[d]	--	Skerfving et al., 1974
16	up to 50	--	65 (45-105)	--	Bakir et al., 1973
48	up to 50	--	--	72[e] (35-189)	Al-Shahristani and Shihab, 1974
6	18-22	--	52	--	Kershaw et al., 1980

[a] Source: U.S. EPA, 1980

[b] Mean

[c] Range

[d] One person had a biological half-time of 164 days. The other four were in the range of 58-87 days.

[e] The data were distributed bimodally. One group accounting for 89% of the samples had a mean value of 65 days, and the other group had a mean value of 119 days.

intake by the volunteers was from 18-22 μg Hg/kg bw. The peak concentration of mercury in the blood occurred at 4.7-14 hours with peak levels of 41-57 μg Hg/ℓ blood. Disappearance of mercury from the blood was biphasic. The fast component (20-30 hours), which had a half-life of 7.6±0.8 hours, represented clearance from the blood as the mercury distributed to various tissues of the body. The slower phase of disappearance of mercury from the blood had a half-life of 51.9±1.5 days. The average red cell-to-blood plasma concentration ratio was 21:1. The fraction of the dose in blood volume was 5.9±0.4%. Using the kinetic parameters the relationship of steady-state blood concentration to daily intake was B = 0.9d, where B equaled steady-state blood concentration in μg Hg/ℓ and d was average intake as μg/day/70 kg bw.

The biological half-time of methyl mercury in the brain is not well described in man, but a study by Aberg et al. (1969) using human volunteers indicates that the half-time is in the same range as that observed in blood and in the whole body (see Table III-2). Whether or not the half-times in the brain and blood are identical is an important consideration in the decision to use blood as an indicator medium for brain concentrations.

As mentioned earlier, methyl mercury is secreted in mother's milk at a concentration averaging ~5% of blood concentration (Bakir et al., 1973). Although half-time in blood is lower in lactating females, the amount of mercury secreted in milk would make a negligible contribution for total excretion and therefore cannot account for the more rapid elimination of mercury by this group (Greenwood et al., 1978).

Other Organo Mercurials. In contrast to short-chain alkyl mercurials, the rate of excretion of mercury is generally greater in experimental animals receiving doses of phenyl or alkoxyalkyl mercurials (Clarkson, 1972a,b). This is in agreement with a rapid conversion to inorganic mercury. The mercurial diuretics generally have half-times considerably shorter than that reported for inorganic mercury because of the rapid excretion of the intact mercurial.

Mathematical Models of Mercury Accumulation in Man

The body will continue to accumulate mercury so long as intake is greater than excretion, until a steady state is reached where intake and excretion are in balance. The progress of accumulation can be described in terms of biological half-time, provided transport and distribution in the body occurs more rapidly than elimination. The WHO Expert Committee (1976) has summarized the mathematical expression relating biological half-time and accumulation in man.

Following dosing, disappearance of mercury from the blood is biphasic. As indicated previously, a fast component with a half-life of 7.6 hours represents distribution to various tissues (Kershaw et al., 1980). Once distribution is completed, elimination follows a single exponential first-order function and the concentration in the organ at any one time can be summarized by the following equation:

$$C = C_0e^{-bt}$$

where: C = concentration in the organ at time t.
C_0 = concentration in the organ at time 0.
b = elimination constant, and
t = time.

The relation between the elimination constant and half-time is the following:

$$T = (\ln 2)/b$$

where: T = biological half-time
$\ln 2$ (natural logarithm of 2) = 0.693

If data on exposure and absorption of the metal are known, then it is possible to predict the body burden of metal at a constant exposure over different time periods. The following expression gives the accumulated amount of metal in the total body (or organ):

$$A = (a/b)(1-e^{-bt})$$

where: A = accumulated amount
a = amount taken up by the body (or organ) daily.

At steady state the following applies:

$$A = a/b$$

The preceding equations can be used to estimate steady-state body burdens, time to reach steady state and time to reach pre-exposure values.

If the half-life of CH_3Hg^+ is 69 days, then

$$T = \frac{\ln 2}{b} ; 69 = \frac{\ln 2}{b} ; b = \frac{\ln 2}{69} = 0.01 \text{ days}^{-1}$$

In five half-lives, the ratio of accumulated metal to the steady-state level will be:

$$\frac{A}{A^1} = \frac{(a/b)\ (1-e^{-bt})}{(a/b)} = 1-e^{-bt}$$

$$\frac{A}{A^1} = 1-e^{(-0.01)(5x69)} \sim 0.97$$

Thus at a constant daily intake, slightly less than 1 year will be required to achieve 97% of steady-state levels. By use of the equation $C = C_0-e^{-bt}$, it can be seen that body burdens will decline to 3% of initial values 345 days, or 5 half-lives, after cessation of exposure. For a half-life of 69 days the accumulated amount at steady-state equals $a/b = a/0.01$ or 100 times the daily intake.

If a separate 45-day half-time, such as that reported for inorganic mercury (Rahola et al., 1971) is assumed, 97% of the steady-state body burden will be reached withing 7.5 months with a steady-state body burden equaling 65 times the daily intake.

Summary

An average absorption of inorganic mercury in the GI tract was determined to be ~7% in humans following oral exposure. The absorption for mice was lower, averaging 1-2%. Kostial et al. (1978) reported that the rate of absorption varied with age. One-week-old mice absorbed 38% of the mercury dose while adult mice showed only 1% absorption. The absorption rate for methyl mercury, ethyl mercury and phenyl mercury is virtually complete while

Friberg and Nordberg (1973) determined that <0.01% of ingested metallic mercury was absorbed in the GI tract.

Nearly all the mercury entering the body becomes bound to thiol groups in proteins and other biological membranes. Mercury, and in particular in organic mercury, tends to accumulate in renal cortical tissue. Inorganic mercury is distributed throughout the body nonuniformly as a result of accumulation in the kidney. Mercuric mercury is distributed by the bloodstream with little accumulation in the brain. Methyl mercury, on the other hand, easily penetrates all membranes and thus may accumulate in the brain several days after exposure. Methyl mercury may also transfer across the placenta. Fetal blood cells have been reported to contain up to 30% more methyl mercury than maternal blood cells. Methyl mercury has also been shown to accumulate in hair with the ratio of inorganic to organic mercury being 0.213.

Aryl and alkoxyalkyl mercury compounds are unevenly distributed in the body with the kidney serving as the primary organ of accumulation following conversion to the inorganic form. Prior to that conversion, the liver is the primary organ for accumulation.

The elimination of inorganic mercury appears to be through urinary excretion. This may be a result of kidney damage. The major route of elimination for methyl mercury is by the fecal route. Other routes include urinary and biliary excretion. THe form of mercury in the feces is inorganic; ~90% of the mercury in the urine is also inorganic. A substantial amount of methyl mercury is found in biliary excretion.

In a mathematical model to determine mercury accumulation in man, it was estimated that a constant daily intake of mercury for 7.5 months would be required to reach a 97% steady-state level.

IV. HUMAN EXPOSURE

Humans may be exposed to mercury in drinking water, food and air. Detailed information concerning the occurrence of and exposure to mercury in the environment is presented in another document entitled "Occurrence of Mercury in Drinking Water, Food and Air" (Letkiewicz et al., 1984). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to mercury from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various mercury concentrations. The 70 kg man is used for estimating intake.

Drinking Water. Based on the compliance monitoring data presented in FRDS (1984), it can be estimated that over 265,000 people are exposed to mercury levels in drinking water exceeding the current MCL of 2 μg/ℓ, distributed as shown below:

Mercury Level (μg/ℓ)	Number of People Exposed
>2-5	204,490
>5-10	51,357
>10-20	9,906
>20	836

The exposure estimates above include a reported exposure of over 92% of the population (247,500 people) from six surface water supplies; 66% (177,000 people) are exposed from a single surface water supply to a mercury level of 3.8 μg/ℓ. The highest exposure level was reported as 100 μg/ℓ, which was a groundwater supply serving 836 people.

The data available are too limited to develop a reliable profile of human exposure to various levels of mercury in drinking water below the current MCL. Also, the available data do not provide for a distinction between exposure to organic and inorganic forms of mercury.

Diet. Several estimates of dietary intake of mercury in the United States have been reported for recent years. The Food and Drug Administration (FDA) includes mercury along with the contaminants analyzed for in its Total Diet Studies ("Market Basket Surveys"). Table IV-1 presents the daily intake estimates for the adult male for several years as reported in recently published Total Diet Studies (FDA, 1980, 1982). As shown in Table IV-1, no particular trend in mercury intake is apparent over the 6 years for which data are provided.

Data obtained in the 1979 Total Diet Study for the adult male (FDA, 1982) indicate that mercury was present in all 12 of the food groups categorized by FDA. Almost 91% of the total intake came from two of the food categories: meat, fish and poultry (73.6%) and beverages (16.9%). FDA has indicated that fish and seafood are the predominant source within the meat, fish and poultry category.

Air. There are few published estimates of the respiratory intake of mercury. The intake of ambient mercury by the U.S. population was estimated by Perwak et al. (1980) for various outdoor inhalation routes (rural, urban and near source exposures) as well as indoor inhalation. The estimates present intakes for concentrations in air ranging from 5-1500 ng/m^3. U.S. EPA (1984) estimated intake for what was presented as an average atmospheric concentration of 20 ng/m^3. These estimates are presented in Table IV-2. U.S. EPA (1984) also reported that atmospheric concentrations are unlikely to exceed average values of 50 ng/m^3, although an intake value for an atmospheric concentration of 1500 ng/m^3 is included in the table. An absorption rate of 80% of the inhaled intakes was reported by U.S. EPA (1984) and was used for the absorbed dose calculations in Table IV-2.

Summary

It is not possible to develop a detailed profile of the population having drinking water, dietary and respiratory intakes of mercury at various

TABLE IV-1

Summary of FDA Total Diet Study Estimates for Mercury Intake for the Adult Male*

Fiscal Year	Intake (μg/day)
1979	5.2
1978	3.4
1977	6.3
1976	6.5
1975	3.7
1974	2.4

*Source: FDA, 1980, 1982

TABLE IV-2

Estimated Exposure of Humans to Mercury in Air[a]

Route	Exposure (μg/day)		Form	Subpopulation	Assumptions[c]
	Intake	Absorbed[b]			
Inhalation					
Outdoors					
Rural	0.1	0.08	Mercury vapor	Large	5 ng/m^3 in air,
Average[d]	0.4	0.32	Mercury vapor	Large	20 ng/m^3 in air,
Urban	0.6	0.5	Mercury vapor	Large	30 ng/mm^3(max.) in air
Near sources	3-30	2.4-24	Mercury vapor	Small	150-1500 ng/m^3 in air
Indoors	2-4	1.6-3.2	Mercury vapor	Large	100-200 ng/m^3 in air

[a] Source: Perwak et al., 1980 (except as otherwise noted)

[b] An 80% absorption of inhaled mercury was assumed.

[c] A respiratory rate of 20 m^3/day was assumed.

[d] From U.S. EPA (1984)

levels. For drinking water, it is possible to estimate the size of the population exposed to levels in public water supplies above 2 μg/ℓ, the current MCL, but not for various levels at or below 2 μg/ℓ. Consequently, a detailed relative source contribution assessment that describes the importance of each medium as a mercury source for different segments of the U.S. population could not be developed.

While it is not possible to develop a detailed profile of human exposure to mercury and the relative source contributions from the three media of interest, it is possible to illustrate the relative importance of each source for various assumed exposure conditions. Table IV-3 presents an illustrative relative source contribution assessment for mercury for the adult male. The intake values for air and food shown in Table IV-3 are based on the intakes presented in the Exposure Estimation Section, above. Six separate intake levels for drinking water, one intake level for food, and four levels for air are presented in Table IV-3.

The calculations shown in Table IV-3 suggest that, for the adult male, food is generally the predominant source accounting for about 60% of the total intake for individuals exposed to drinking water with mercury levels below 2 μg/ℓ, which appears to be the majority of the population. Drinking water significantly exceeds food as the predominant source of exposure for the adult male only at mercury levels near 5 μg/ℓ or greater, which is more than twice the current MCL.

TABLE IV-3

Relative Source Contribution Assessment for Mercury for the 70 kg Adult Male: Total Intake (ug/kg/day) from Drinking Water, Air and Food[a] (Percent from Drinking Water)

Drinking Water Concentration (μg/ℓ)	Drinking Water Intake[b] (μg/kg/day)	Air Intake (μg/kg/day) Rural[c] (0.001)	Air Intake (μg/kg/day) Average[d] (0.005)	Air Intake (μg/kg/day) Urban[e] (0.007)	Air Intake (μg/kg/day) Source Dominated[f] (0.34)
0	0	0.075 (0%)	0.079 (0%)	0.081 (0%)	0.41 (0%)
0.5	0.014	0.089 (16%)	0.093 (15%)	0.095 (15%)	0.43 (3%)
2	0.057	0.13 (44%)	0.14 (41%)	0.14 (41%)	0.47 (12%)
5	0.14	0.22 (64%)	0.22 (64%)	0.22 (64%)	0.55 (25%)
10	0.29	0.36 (81%)	0.37 (78%)	0.37 (78%)	0.70 (41%)
20	0.57	0.64 (89%)	0.65 (88%)	0.65 (88%)	0.98 (58%)

[a] Assumes a constant food intake of 5.2 μg/day, or 0.074 μg/kg/day; 100% absorption.

[b] Assumes 2 ℓ/day consumption; 100% absorption

[c] Assumes exposure to 5 ng/m³; 20 m³/day ventilation rate; 80% absorption

[d] Assumes exposure to 20 ng/m³; 20 m³/day ventilation rate; 80% absorption

[e] Assumes exposure to 30 ng/m³; 20 m³/day ventilation rate; 80% absorption

[f] Assumes exposure to 1500 ng/m³; 20 m³/day ventilation rate; 80% absorption

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V. HEALTH EFFECTS ON ANIMALS

Introduction

This chapter will cover mercuric salts and short-chain alkyl mercurials. Methyl mercury and other short-chain alkyl mercury compounds have been used extensively in the past as fungicides and are of concern to human health because of their high degree of bioconcentration in aquatic species. Mercury salts may be ingested directly in drinking water but are probably of greater concern because of potential biotransformation to methyl mercury. Hundreds of aryl and alkoxyalkyl mercury compounds have been synthesized in the past, mostly as pharmaceutical agents. Except for a few phenyl mercury compounds found in fungicides, these mercurials are generally obsolete and do not pose a water pollution problem. Coverage of these compounds will therefore be very brief. Liquid metallic mercury will not be covered because it is nontoxic even at very high doses. Inhaled mercury vapor will not be covered because it does not contribute significantly to body burdens (U.S. EPA, 1980).

Acute Effects

Information on the LD_{50}s of all types of mercury compounds has been reviewed by a Swedish Expert Group (1971), and for aryl and alkoxyalkyl mercurials by Goldwater (1973). The results reported for the different mercury compounds are not easily compared since different animal species and different routes of administration have been used. Despite all these differences, the LD_{50} generally lies between ~10 and 40 mg/kg body weight for all compounds tested to date including inorganic mercury, alkyl mercury, aryl mercury and alkoxyalkyl mercury compounds.

This similarity in the LD_{50}s of the various types of mercury compounds can be attributed to the fact that when given in acute doses in excess of 10 mg/kg, mercury in any chemical form will denature proteins, inactivate enzymes and cause severe disruption of cellular processes in any tissue with which it comes into contact in sufficient concentration. The symptoms of acute toxicity usually consist of shock, cardiovascular collapse, acute renal failure and severe damage to the GI tract.

Kidney Effects

The toxic effects of organic and inorganic compounds of mercury upon the kidney are listed in Table V-1.

Inorganic Mercury Compounds. The rat has proven to be especially sensitive to the effects of mercury on the kidneys; damage occurs in this species at doses below that resulting in neurological manifestations. In a group of similarly designed experiments (Bariety et al., 1971; Druet et al., 1978; Makker and Aikawa, 1979; Weening et al., 1978), rats were injected s.c. three times weekly for up to 8 months with doses of inorganic mercury ranging from 0.05-2.5 mg/kg/injection (0.02-1.07 mg/kg/day). The animals developed renal damage characterized by an initial production of antiglomerular basement membrane antibodies, followed by the appearance of immune-complex deposits in the glomerular tufts and small renal arteries accompanied by proteinuria and hypoalbuminemia. At higher doses glomerular pathology could be detected. Fixation of anti-rat IgG antiserum could be detected even at the lowest dose levels (0.02 mg/kg/day), while proteinuria and hypoalbuminemia were detected at 0.04 mg/kg/day (Druet et al., 1978). This immune response occurred only in a genetically susceptible strain of rats.

TABLE V-1

Toxic Effects of Inorganic and Organic Mercury Compounds upon the Kidney in Animals

Species	Compound	Dose* (mg/kg/day)	Duration of Treatment	Route of Exposure	Critical Effects	Reference
Rat	mercuric chloride	0.2, 0.4, 0.6, 1.1	up to 8 months	subcutaneous	Glomerulonephritis proteinurea at doses of 0.6 and above	Barlety et al., 1971
Rat	mercuric chloride	0.6	27 weeks	subcutaneous	Glomerulonephritis deposition of IgG, IgM and C_3 in glomeruli	Makker and Aikawa, 1979
Rat	mercuric chloride	0.4-0.6	up to 14 weeks	subcutaneous	Glomerulonephritis immune complex deposition	Weening et al., 1978
Rat	mercuric chloride	0.02, 0.04, 0.11, 0.20, 0.43, 0.86	up to 12 weeks	subcutaneous	Proteinuria at doses down to 0.04. Fixation of antiserum at lowest dose	Druet et al., 1978
Rat	mercuric acetate	0.025, 0.125, 0.5, 2, 8	2 years	oral	Glomerulonephritis at doses of 2 and 8 mg/kg/day	Fitzhugh et al., 1950
Rat	phenylmercuric acetate	0.005, 0.025, 0.125, 0.5, 2, 8	2 years	oral	Glomerulonephritis at doses down to 0.025 mg/kg/day	Fitzhugh et al., 1950
Pigs	phenylmercuric chloride	0.19, 0.38, 0.76, 2.3, 4.6	up to 3 months	oral	Glomerulonephritis at 2.3 and 4.6 mg/kg/day	Tryphonas and Nielsen, 1970
Rats	methylmercury hydroxide	2 and 10	5-7 days	subcutaneous	Focal necrosis of tubular epithelium	Klein et al., 1972, 1973
Rats	methylmercury dicyandiamide	0.6, 1.2, 2.4	up to 12 weeks	oral	Inflammation and fibrosis of kidney cortex at all doses	Magos and Butler, 1972
Rat	methylmercury chloride	0.1	12 weeks	oral	Extrusion of numerous cytoplasmic masses into the kidney proximal tubule	Fowler, 1972

*If ppm was reported, mercury intake was estimated based on food intake for rats of 5% of body weight/day.

Fitzhugh et al. (1950) exposed weanling rats, 10-12 animals/sex/group to mercuric acetate at concentrations of 0.5, 2.5, 10, 40 and 160 ppm in the diet. The concentration was listed as mercuric acetate and not mercury. The daily intakes were estimated to approximate 0.025, 0.125, 0.5, 2.0 and 8.0 mg/kg bw mercuric acetate based upon consumption of an amount of food equal to 5% of bw/day. Microscopic examination of a variety of tissues indicated that the kidney was the only organ affected to any degree with lesions originating in the proximal convoluted tubules. The lowest dose resulting in detectable effects was 40 ppm (~2 mg/kg). Unfortunately many animals died during the course of the study. Moreover, the authors did not report the numbers of animals examined per group or attempt to quantitate the results. Based on the total number of animals examined it appeared that the final group sizes averaged about 5, a minimally adequate group size for this type of study.

Miura et al. (1981) reported detectable lesions in the proximal tubular cells of the kidney after a single i.p. injection of only 1 μM $HgCl_2$ (0.2 mg/kg as Hg) in male rats. Accumulation of mercury in the kidneys, however, indicated that the absorption efficiency was much greater than would be expected from the GI tract. Thus, the s.c. route may not be appropriate for defining threshold values unless accurate estimates of absorption are known for both oral and subcutaneous treatment.

Methyl mercury. The principal effect of methyl mercury is on the nervous system. However, kidney damage is also known to occur. Magos and Butler (1972) fed rats methyl mercury dicyandiamide 5 days/week for 59 days and reported extensive kidney damage to the cortex with extensive inflammatory reaction surrounding the cortex and some early fibrosis even at the lowest dose of 0.6 mg/kg/day. Klein et al. (1972) reported tubular degeneration after s.c. injection of 10 mg/kg/day into rats for 7 consecutive days. In a follow-up study focal lesions were detected in the kidney cortex as early as day 6 following daily injections of 10 mg/kg/day and as early as day 11 following injections of 2 mg/kg/day (Klein et al., 1973). Finally, Fowler (1972) found that feeding methyl mercury chloride (0.1 mg/kg) daily for up to 12 weeks resulted in extrusions of numerous cytoplasmic masses from kidney proximal tubules, despite apparently normal glomeruli. The authors suggested that such occurrences can explain the proteinuria observed in occupationally-exposed persons.

In contrast to effects of mercury on rats, kidney damage was not reported in cats exposed to as much as 0.45 mg/kg (Albanus et al., 1972; Chang et al., 1974; Charbonneau et al., 1976; Grant, 1973), or in monkeys exposed to either 0.05 mg/kg bw/day (Rice and Gilbert, 1982) or to doses resulting in blood levels of up to 4 μg/mℓ blood (Berlin et al., 1973; Evans et al., 1977).

Overall the rat appears to be more sensitive to the effects of mercury compounds than other species. While some authorities consider the rat as a poor model for the effects of mercury on man, this criticism is often based on the rat's lack of sensitivity to nervous system effects rather than a greater degree of sensitivity to kidney damage. Studies by Kazantzis et al. (1962), however, indicate that some workers chronically exposed to a variety of mercury compounds are quite sensitive to kidney damage and show many of the same effects seen in rats. These workers may represent a genetically sensitive subpopulation similar to the sensitive strain of rats.

Klein et al. (1973) suggested that the pathological effects of mercury on the kidney were due to biotransformation to the inorganic form. At a 2 mg/kg/day dose, 31% of the total mercury in the kidneys was present in the inorganic form after 6 days; by day 11 it had risen to 38%. The results of the study by Magos and Butler (1972) also tend to suggest that effects may have been due to transformation since only 65% of the mercury present in the kidney during subchronic oral administration was present in the organic form versus 95% in the brain, 95% in the blood and 92% in the liver.

Aryl and Alkoxyalkyl Mercury Compounds. In the Fitzhugh et al. (1950) study, discussed earlier, rats were fed phenyl mercury acetate as well as mercury acetate for 2 years. Daily intakes for the phenyl compounds were estimated to equal ~0.005, 0.025, 0.125, 0.50, 2.0 and 8.0 mg/kg/day. Growth was retarded at 2 mg/kg in both sexes, while 0.5 mg/kg retarded growth in males. As little as 0.025 mg/kg resulted in detectable renal effects in the form of moderate tubular changes in females; in males, effects were detected at 0.125 mg/kg. By contrast, the smallest dose of mercuric acetate causing detectable effects was 2 mg/kg/day. The changes noted at low concentrations appeared to be an intensification of changes occurring in controls as part of the aging process. Goldwater (1973) criticized this study because of small group sizes and the apparent differing sensitivity between sexes despite an approximately equal storage in males and females. Tryphonas and Nielsen (1970) fed weanling piglets phenyl mercuric chloride at daily doses equivalent to 0.19, 0.38, 0.76, 2.28 and 4.56 mg/kg bw. Decreased weight gains, but no pathological lesions were detected in the 0.76 mg/kg group. Weight loss, diarrhea, necrosis of intestinal walls and kidney pathology were the primary effects detected at the two highest doses.

Compared with the phenyl mercury compounds, much less is known about the chronic effects of alkoxyalkyl mercury compounds. Baer and Beyer (1966) reported that these compounds, which are closely related to the mercurial diuretics, might be expected to have a low order of toxicity because of ready liberation and rapid excretion of their mercury. Merville et al. (1967) found that doses of 1-3 mg/kg of methoxyethyl mercuric chloride injected i.p. had patterns of elimination and accumulation of mercury in the kidneys similar to that of phenylmercuric acetate.

Neurotoxicology

Inorganic Mercury Compounds. Since inorganic salts do not penetrate the blood-brain barrier as well as the alkylmercury compounds (Jugo, 1976) and tend to accumulate to a large extent in the kidney (Rothstein and Hayes, 1960), studies relating to the toxicology of these compounds have usually focused on the kidneys. One exception has been the investigations of Chang and Hartmann (1972a,b). In a short-term study using rats they reported that a single 1 mg/kg dose either orally or by s.c. injection resulted in leakage of dye into the nervous parenchyma within 12 hours post-treatment, indicating that mercuric chloride can increase the permeability of the blood-brain barrier.

In a series of subchronic experiments (Chang and Hartmann, 1972b), rats were exposed to mercuric chloride, 1 mg/kg/day, by intubation or s.c. injection for up to 11 weeks. The rate of body weight gain was decreased after 20 days and actual weight loss occurred after 65-70 days. Neuropathological effects were first detected after 2 weeks exposure. These consisted of peripheral vacuolization of cells in the dorsal root ganglia, followed by the development of multiple small lesions in the ganglia.

The rate of development of mercuric chloride effects and the degree of change were less than noted in other groups of rats treated with identical doses of methyl mercury chloride. This indicates that alkyl mercury compounds are more toxic to the nervous system. Also of note was the finding that s.c. treatment produced very similar results compared with the oral route for either compound.

Methyl mercury Chloride. The effects of methyl mercury on the nervous system are summarized in Table V-2. As was reported for mercuric chloride (Chang and Hartmann, 1972a), a single dose of 1 mg/kg methyl mercury chloride, either orally or by s.c. injection, in rats resulted in leakage of dye into the nervous parenchyma of the brain as early as 12 hours post-treatment. A single i.p. injection of 10 mg/kg methyl mercury in rats inhibited protein synthesis in neurons from the cerebrum, cerebellar granule cells and Purkinje cells within 2 days. All except the granule cells showed a rebound to above control levels within 1 week after treatment (Syversen, 1977).

Klein et al. (1972) administered 10 mg/kg bw methyl mercury chloride daily s.c. for up to 7 days and then held the rats for an additional 8 days. Weight loss occurred by 6-8 days with neurological manifestations such as decreased activity, ataxia, and weakness along with pathological changes in the brain apparent by day 15. Similar treatment by Omata et al. (1978, 1980a) for 7 consecutive days resulted in the detection of gross neurological symptoms by days 9-11. Protein synthesis in the cerebral cortex decreased 15-32% during the asymptomatic phase and decreased even more during the symptomatic stages. Oral doses of 5 or 7.5 mg/kg in rats for 8 consecutive days resulted in neurological effects by day 8 with the high dose

TABLE V-2

Effects of Methyl mercury Exposure upon Neurotoxicology in Animals

Species	Dose (mg/kg/day)	Duration of Treatment	Route of Exposure	Critical Effects	Reference
Rat	1	single dose	oral and subcutaneous	Leakage of dye into brain	Chang and Hartmann, 1972a
Rat	10	single dose	intraperitoneal	Decreased protein synthesis in the brain	Syversen, 1977
Rat	10	7 days	subcutaneous	Weight loss; neurological symptoms	Klein et al., 1972
Rat	10	7 days	subcutaneous	Weight loss; neurological symptoms, decreased protein metabolism	Omata et al., 1978 1980a
Rat	5, 7.5	8 days	oral	Neurological symptoms	Cavanagh and Chen, 1971a
Rat	5.3	14 days	intraperitoneal	Decreased oxygen uptake and enzyme activity in the brain	Yoshino et al., 1965
Rat	0.3, 1.0, 3.3	15 days	oral	Decreased synthesis of dopamine	Sharma et al., 1982
Rat	1, 2.5, 5	21 days	subcutaneous	Increased dopamine and norepinephrine uptake, decreased brain weight	Bartolome et al., 1982
Rat	1.4	up to 29 days	subcutaneous	Neurological symptoms	Somjen et al., 1973a,b
Rat	0.6, 1.2, 2.4	8 weeks	oral	Behavioral changes, neuropathology; effects marginal at the lowest dose	Magos and Butler, 1972
Rat	1	11 weeks	oral and subcutaneous	Lesions of dorsal root ganglia	Chang and Hartmann, 1972b
Pigeon	0.7, 1.1, 1.4	up to 77 days	oral	Decreased rate and accuracy of pecking at all doses	Evans et al., 1982
Cat	0.45	up to 83 days	oral	Behavioral changes; convulsions	Albanus et al., 1972
Cat	0.45	up to 83 days	oral	Brain cortex pathology	Grant, 1973
Cat	0.01	11 months	oral	Behavioral changes; focal liver lesions	Chang et al., 1974; Chang and Yamaguchi, 1974

TABLE V-2 (cont.)

Species	Dose (mg/kg/day)	Duration of Treatment	Route of Exposure	Critical Effects	Reference
Cat	0.003, 0.008, 0.020, 0.046, 0.074, 0.176	2 years	oral	Behavioral changes, lowest dose resulting in detectable effects was 0.046; convulsions at higher doses	Charbonneau et al., 1976
Monkey	doses resulting in 0.75-2 μg/g in blood	up to 122 days	oral	Behavioral changes, threshold levels were between 0.75 and 1.2 μg/mL blood	Berlin et al., 1973
Monkey	doses resulting in* 1-4 μg/g in blood	up to 1000 days	oral	Reduced sensitivity to visual stimuli, tremor upon reaching for small objects, constriction of visual field	Evans et al., 1977
Monkey	0.05	3-4 years	oral	Impaired spatial vision	Rice and Gilbert, 1982

*In the Evans study four or five priming doses of 1 mg/kg at 5-day intervals followed by weekly doses equivalent to intakes of 0.06-0.08 mg/kg/day were used for stumptail and pigtail monkeys. Squirrel monkeys received a single priming dose of 1 or 2 mg/kg followed by maintenance doses equivalent to 0.014-0.028 mg/kg/day.

and by days 12-13 with the 5 mg/kg dose. Pathological changes were detected in the brain at about the same time (Cavanagh and Chen, 1971a).

Yoshino et al. (1966) injected a mean dose of 5.3 mg/kg/day i.p. of methyl mercury thioacetamide into rats for up to 14 days and classified them into two groups; those with neurological symptoms and those which were asymptomatic. A decrease in oxygen consumption in the brain along with a decrease in the activities of some sulfhydryl enzymes was noted only in rats exhibiting symptoms. The synthesis of dopamine was decreased in rats fed 1, 3 or 10 mg/kg bw methyl mercury every 3 days (0.3, 1.0 or 3.3 mg/kg/day) for 15 days. This effect was noted even at the lowest dose, although this amount did not result in overt neurological symptoms (Sharma et al., 1982).

Subcutaneous injection of 2 mg/kg methyl mercury hydroxide, 5 days/week for up to 29 days in rats resulted in neurological symptoms such as ataxia and abnormal reflexes by the third or fourth week of treatment (Somjen et al., 1973a). Oral doses of methyl mercury dicyandiamide 5 days/week at levels of 3.36, 1.68 and 0.84 mg/kg bw (2.4, 1.2 and 0.6 mg/kg/day mean daily dose over 7 days) for up to 59 days resulted in clearcut neurological effects at the two higher doses. At 0.6 mg/kg/day, 2/16 animals showed a slight degree of ataxia along with some histopathology of the cerebellum after 8 weeks (Magos and Butler, 1972). Treatment of rats daily for up to 11 weeks with 1 mg/kg bw methyl mercury chloride, orally or s.c., resulted in the detection of neurological changes along with brain histopathology within 1 week from the start of treatment (Chang and Hartmann, 1972b).

Miyama et al (1983) fed male Wistar rats a diet containing either 10 or 20 ppm methyl mercury chloride (~0.5-1.0 mg/kg) for up to 16 weeks. The earliest detectable effect was a reduction in the amplitude of a sensory nerve pulse, occurring in 4-5 weeks in the 20 ppm group and 8-9 weeks in the 20 ppm group. Termination of weight gain and a decrease in nerve conduction velocity occurred after 5-6 weeks in the 20 ppm group and 9-12 weeks in the 10 ppm group, while gross neurological symptoms were noted after 6-8 weeks and 13.5-15.5 weeks for the high and low dose groups, respectively.

The sensitivity of pigeons to methyl mercury appeared to be comparable to that of rats. Daily oral doses of 0.7, 1.1 and 1.4 mg/kg bw Hg resulted in a decreased rate and accuracy of pecking after 41, 49 and 65 days for the high, medium and low doses, respectively (Evans et al., 1982).

The cat was used in several investigations to test the toxicity of methyl mercury by a common means of human exposure; contaminated fish. Albanus et al. (1972) reported progressive behavioral changes in cats beginning on days 4-11 and culminating in convulsions after 60-83 days exposure to 0.45 mg/kg/day methyl mercury. The results were not affected by the method of exposure, either feeding fish containing mercury bioconcentrated from contaminated water or adding methyl mercury chloride directly to the fish meal. Grant (1973) evaluated cortical damage in the same group of cats. Definite cortical damage was seen in animals having a blood concentration ≥1.2 mg/ℓ Hg, but none was detected if the concentration was ≤0.75 mg/ℓ Hg.

Charbonneau et al. (1976) fed methyl mercury chloride to cats at doses of 0.003, 0.008, 0.020, 0.046, 0.074 and 0.176 mg/kg/day for 2 years. The lowest concentration resulting in detectable behavioral symptoms occurred in the 0.046 mg/kg/day group after 60 weeks. The symptoms were mild and not progressive. At the two highest doses behavioral changes were progressive, sometimes culminating in convulsions. Pathological changes in the nervous system were restricted to the dorsal root ganglia and were not seen at doses <0.074 mg/kg/day.

Berlin et al. (1973) exposed squirrel monkeys for varying periods of time up to 122 days to repeated oral doses of methyl mercury chloride. Although the dose levels resulting in detectable changes are uncertain, these investigators found that the threshold for both behavioral and CNS pathology occurred at a blood concentration range of 0.75- 1.2 mg/ℓ.

Evans et al. (1977) exposed stumptail monkeys (*Macaca arctoides*), pig-tail monkeys (*Macaca nemestrina*) and squirrel monkeys (*Saimura sciureus*) orally to methyl mercury chloride for up to 1000 days. Macaques received priming doses of 1 mg/kg bw, at 5-day intervals, 4 or 5 times followed by prolonged intake equivalent to 0.06-0.08 mg/kg/day. Squirrel monkeys received only a single priming dose of 1 or 2 mg/kg followed by maintenance doses equivalent to 0.014-0.028 mg/kg/day. This dosage regime was designed to maintain blood mercury at 1-4 mg/ℓ blood. The critical effects were reduced sensitivity to visual stimuli at low luminescence and intention tremor upon reaching for a small object. All monkeys with a blood concentration of >2 mg/ℓ developed symptoms with latent periods ranging from <20 days to 200 days. At 1.0-2.0 mg/ℓ, 5/6 developed overt signs within 1000 days with a latent period of 135-450 days. One monkey with a blood Hg between 0.5 and 1.0 mg/ℓ developed symptoms at about 200 days.

Previous studies have described effects of methyl mercury chloride upon the mature nervous system. A limited number of animal studies as well as human exposures, which will be described in Chapter VI, indicate that the developing nervous system may be more sensitive to the effects of methyl mercury than after maturity.

Bartolome et al. (1982) found that in newborn rats injected s.c. daily with 5 mg/kg bw methyl mercury chloride for 21 days the rate of brain weight increase was significantly less than controls. Levels of 1 and 2.5 mg/kg, which did not affect brain weights, still resulted in increased uptake and turnover of both dopamine and norepinephrine.

Chang et al. (1974) and Chang and Yamaguchi (1974) fed kittens tuna containing 0.3-0.5 ppm methyl mercury chloride for 11 months. The total mercury intake over the period averaged 6.3 mg/cat or ~19 μg/day. Neurological disturbances could be observed after 7-11 months. Following sacrifice, focal lesions could be detected in the liver as well as the brain. Body weights were not reported but if a mean weight/animal of 2 kg is assumed over the period, the intake would average ~0.01 mg/kg/day. This would indicate that kittens are extremely sensitive to the toxic effects of methyl mercury chloride.

Rice and Gilbert (1982) fed cynamolgous monkeys methyl mercury at doses of 0.05 mg/kg/day for 3-4 years starting at birth. Blood concentrations of mercury peaked at 1.2-1.4 mg/ℓ, then declined after weaning to a steady level of 0.6-0.9 mg/ℓ. No overt signs of toxicity were noted, but when tested after 3-4 years of age, the monkeys exhibited impaired spatial vision under conditions of both high and low luminescence.

As can be seen in Table V-2, the effective dose of methyl mercury for producing neurological symptoms varies considerably among species. The brain-to-blood ratio of mercury also varies with species. Examples illustrating these differences are shown in Figure V-1. If differences in sensitivity are due to differences in brain-to-blood ratios, then neurological symptoms should occur at similar brain concentrations of mercury among species. Proof of this would allow valid extrapolation from animals to humans based upon mercury concentrations in the brain.

No chronic and few subchronic studies have been conducted in animals at near threshold concentrations of methyl mercury in which brain concentrations were also measured. A few chronic studies using monkeys and cats, in which blood mercury concentrations were measured, allowing estimation of brain mercury from known brain-to-blood ratios were conducted. Two subchronic studies in which brain mercury concentration was measured directly were also conducted. The results are listed in Table V-3.

In these six studies there does appear to be a fairly close relationship between brain concentration and effects. The low values reported to cause effects in the Rice and Gilbert (1982) study may well have been because the monkeys were exposed from birth, a time when the developing brain is more sensitive to the effects of mercury than the adult brain. On the other

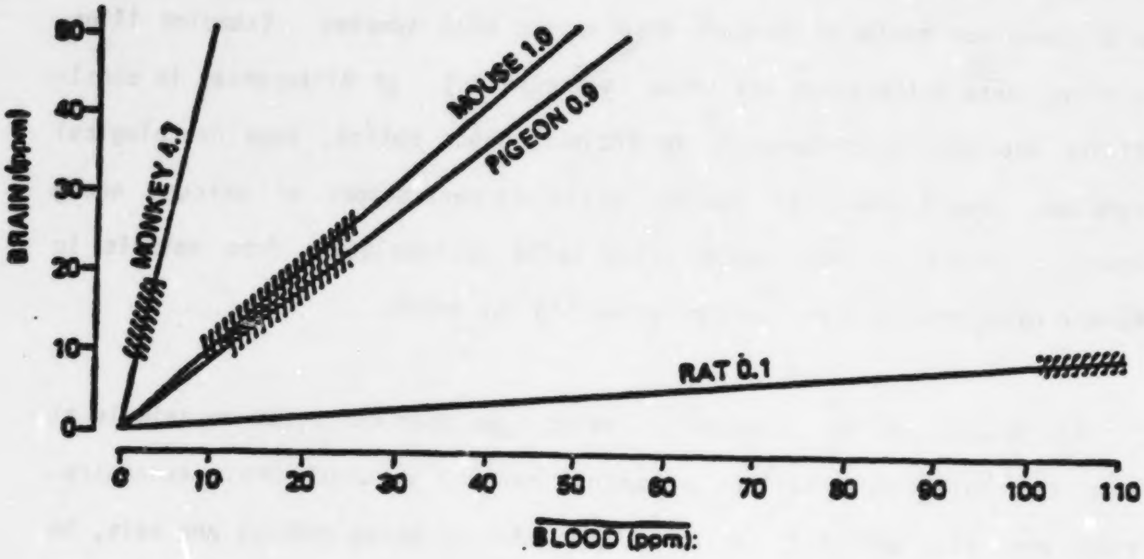

FIGURE V-1

Comprehensive brain/whole blood regression lines in four species orally dosed with methyl mercury. The shaded areas correspond to the onset of the first detectable signs and symptoms of poisoning.

Source: Weiss, 1978

TABLE V-3

Relationship Between Brain Levels of Mercury and Neurological Symptoms at Near Threshold Dosages

Animal	Dose (mg/kg/day)	Brain Concentration (ppm)	Comments	Reference
Monkey	0.057-0.086	~5[a]	At blood levels of 1 ppm the predicted latency period exceeds 200 days	Evans et al., 1977
Monkey	0.050	3-5[a]	Exposure from birth resulted in impaired spatial vision	Rice and Gilbert, 1982
Monkey	not stated	6-7[a]	Visual symptoms began suddenly after 85-115 days	Berlin et al., 1973
Cat	0.046	6-7[b]	Slight, nonprogressive neurological symptoms	Charbonneau et al., 1976
Rat	0.60	6	Neurological symptoms were detected in 2 of 4 animals after 10 weeks. Brain mercury concentration was still rising slowly after 12 weeks.	Magos and Butler, 1972
Pigeon	0.70	12-16	The mean latent period was 65 days	Evans et al., 1982

[a] Brain concentration was estimated as 5 times blood concentration

[b] Brain concentration was estimated to equal blood concentration

hand, the high concentration for the pigeon was probably due to the likelihood that the dose was well above threshold limits. The latency and brain concentration of the pigeons fits the regression curve published by Evans et al (1977) for monkeys, in which a brain concentration of about 5 ppm was predicted for a latency period of 200-300 days (approximate threshold).

In summary, the effects of methyl mercury upon the nervous system occur after a latency period that can be as long as a year or more at near threshold concentrations. Mercury concentrations in the brain appear to be The major determinants of toxicity. Brain-to-blood mercury ratios vary among species with animals having a high ratio; primates are much more sensitive than rats, for example, which have a very low ratio. The immature animal is more sensitve to methyl mercury than adults, probably because low concentrations disrupt brain development.

Aryl and Alkoxyalkyl Mercury Compounds. The toxicology of these compounds was reviewed by Goldwater (1973). Little information is available concerning their effects upon the nervous system. In the study by Fitzhugh et al. (1950) reported earlier, no neurological effects were reported in rats even after feeding phenyl mercury acetate for 2 years at daily doses as great as 8 mg/kg/day. In a similar study with pigs, doses of phenyl mercury chloride up to 4.56 mg/kg/day, which produced definite kidney injury, were not reported to affect the nervous system (Tryphonas and Nielsen, 1970).

Teratogenic and Reproductive Effects

Inorganic Mercury Compounds. Gale and Ferm (1971) studied the teratogenic effects of mercuric acetate on Syrian golden hamsters. Single doses of 2, 3 or 4 mg/kg were injected i.v. on day 8 of gestation. Growth retardation and edema of the fetuses was found at all three dose levels, while an increase in the number of abnormalities was detected at the two higher doses. In a more recent study, Gale (1981) compared the embryotoxic effects of a single s.c. dose of 15 mg/kg mercuric acetate on the eighth day of gestation in five inbred strains of Syrian hamsters. While strain differences were apparent, a variety of abnormalities were reported in all the strains. Gale (1974) also compared the relative effectiveness of different exposure routes in Syrian hamsters. The following sequence of decreasing efficacy was noted for mercuric acetate; i.p. > i.v. > s.c. > oral. The lowest doses used, 2 mg/kg for i.p. and 4 mg/kg for the other three routes, were all effective in causing increased resorption and percent abnormalities.

In male mice administered a single i.p. dose of 1 mg/kg mercuric chloride, fertility decreased between days 28 and 49 post-treatment with no obvious histological effects noted in the sperm (Lee and Dixon, 1975). The period of decreased fertility indicated that spermatogonia were affected. The effects were less severe than following a similar dose of methyl mercury. A single i.p. dose of 2 mg/kg mercury chloride in female mice resulted in a significant decrease in the total number of implants, number of lining implants and a significant increase in the percentage of dead implants (Suter, 1975). These effects suggest that mercury may be a weak inducer of dominant lethal mutations.

Methyl mercury. Histological evidence of brain damage as a result of prenatal exposure to methyl mercury has been reported for several animal species in several early studies (Matsumoto et al., 1967; Nonaka, 1969;

Morikawa, 1961). Oharazawa (1968) reported an increased frequency of cleft palate in mice treated with an alkyl mercury phosphate. Decreased birth rate and possible neurological damage, but no gross teratological effects, were noted in the offspring of mice treated with doses as low as 0.1 mg/kg methyl mercury (Fujita, 1969).

Olson and Massaro (1977, 1980) found that 5 or 10 mg/kg methyl mercury on day 12 of gestation induced a high incidence of delayed palate closure and cleft palate in mice. Harper et al. (1981) induced cleft palate in four inbred strains of mice following i.p. injection of 7.5 mg/kg.

Treatment of 129 Sv/Sl and A/J mice with 2, 4 or 8 mg/kg methyl mercury dicyandiamide i.p. resulted in retardation of fetal growth and an increased resorption of implants in both strains. Teratogenic effects (primarily palate and jaw defects) were detected in the 129 Sv/Sl mice at all doses but in the A strain only at the highest dose (Spyker and Smithberg, 1972). A single dose of 8 mg/kg in 129 Sv/Sl mice also resulted in behavioral deviations in the offspring (Spyker et al., 1972).

Khera (1973) reported that daily oral doses of 1, 2.5 and 5 mg/kg methyl mercury chloride in male rats resulted in a dose-related reduction in mean litter size from matings taking place 12-27 days from the start of treatment. This reduction was attributed to preimplantation losses. No effects of subchronic dosing at 0.1 mg/kg could be detected.

Despite the definite effects on rats, Khera (1973) failed to detect a reduction in fertility of male mice treated with up to 5 mg/kg methyl mercury. Suter (1975) likewise found that treatment of male mice with a single i.p. injection of 10 mg/kg bw methyl mercury hydroxide did not result in a significant change in number of implants, living embryos or dead implants in the female mated with the treated male. Females treated similarly, however, did show a small but significant decrease in the total number of implants as well as number of living implants. Moreover, Lee and Dixon (1975) reported that a single i.p. dose of 1 mg/kg bw methyl mercury hydroxide in male mice resulted in a reduction in fertility at 35-56 days post-treatment, which was almost 100% on day 42.

Aryl and Alkoxyalkyl Mercury Compounds. The only teratogenic information on any of these compounds was reported by Gale and Ferm (1971) in which Syrian golden hamsters were dosed with 5, 7.5, 8 and 10 mg/kg bw phenyl mercuric acetate i.v. on the eighth day of gestation. All except the lowest dose induced increased resorption rates and edema along with a few miscellaneous abnormalities including exencephaly, cleft lip and palate, and rib fusions.

Overall, the relevance of findings of gross anatomic abnormalities in animals given high parenteral doses of mercury to human health risks is wholly unknown.

Mutagenic Effects

The only studies relating to the mutagenic effects of organic mercury compounds are those of Ramel (1972). Methyl mercury hydroxide at doses of 5 mg/ℓ in adult fruit flies (Drosophila melanogaster) induced nondysjunction of chromosomes, but did not appreciably affect enzyme systems responsible for chromosome repair. Both methyl and phenyl mercury appeared to produce small increases in the rate of point mutations. The number of fruit-flies/ℓ was not stated.

Carcinogenicity

When rats were injected i.p. with metallic mercury, sarcomas were observed only in those tissues that had been in direct contact with the metal (Druckrey et al., 1957). Mitsumori et al. (1981) fed groups of SPF ICR mice 15 or 30 ppm methyl mercury in the diet for up to 78 weeks. The majority of the 30 ppm group died by week 26. In the 15 ppm group, the first tumor was seen at week 58. Histopathology on kidney tissue from all animals surviving after 53 weeks revealed renal tumors in 13/16 males in the 15 ppm group. Of these, 11 were classified as adenocarcinomas and 2 as adenomas. One adenoma was detected among 37 control males and no tumors were seen in either control or exposed females. The possible presence of tumors at other sites was not reported in this preliminary communication.

Summary

The primary effect of methyl mercury, except in rats is on the nervous system. Inorganic mercury, on the other hand, is more effective in producing renal damage since it penetrates the brain poorly but is accumulated in the kidneys. Organic mercury compounds of the type R-Hg+ when R is phenyl, substituted phenyl, long chain alkyl or alkyloxyalkyl generally act more similarly to inorganic mercury because of their rapid breakdown *in vivo*.

Short-chain alkyl mercurials, especially methyl mercury, are toxic at lower doses than either larger organic mercury compounds or inorganic mercury. Effects of methyl mercury on the nervous system appear at about the same brain concentration in most species. The developing CNS is more sensitive to the effects of methyl mercury than the mature CNS.

In a single preliminary communication methyl mercury was reported to induce tumor formation in the kidneys of mice. This limited data is not considered sufficient to draw conclusions concerning the carcinogenicity of mercury. The relevance of teratology findings in animals to effects on humans is not established.

VI. HEALTH EFFECTS ON HUMANS

As in the animal health effects chapter, the coverage will be primarily limited to short-chain alkylmercurials, aryl and alkoxyalkyl compounds, and compounds of divalent mercury (Hg^{++}). Health effects of mercury vapor is covered in the final report of the Mercury Health Effects Update (U.S. EPA, 1984).

Greatest emphasis will be placed on those effects occurring at the lowest levels of exposure to mercury and to target organs that suffer effects most hazardous at the lowest exposure.

Lethal Dosages and Effects Following Acute Exposures

Inorganic Mercury Compounds. Troen et al. (1951) reported 18 cases of poisoning from oral intake of single doses of $HgCl_2$ with the common finding of mild to severe erosion of the GI tract. The lowest lethal dose was 29 mg/kg. Gleason et al. (1957) estimated that the lethal oral dose for mercuric salts in man was 1-4 g. This would be equivalent to 14-57 mg/kg for a 70 kg man. Pesce et al. (1977) reported on an attempted suicide by ingestion of 1.5 g $HgCl_2$. Despite emesis about 5 minutes after ingestion, the patient experienced severe abdominal pain with a brief period of unconsciousness. Abdominal pain accompanying any deviation from a bland diet the first few days post-exposure indicated damage to the GI tract.

In the above case reports, in addition to GI damage, acute exposure was characterized by pharyngitis, dysphagia, nausea, vomiting, bloody diarrhea and shock. Later, swelling of the salivary glands, stomatitis, loosening of the teeth, nephritis, anuria and hepatitis occurred. Death was usually caused by shock, cardiovascular collapse, acute renal failure and severe GI damage.

Methyl and Short-Chain Alkylmercurials. The acute lethal dose of methyl mercury in humans has not been determined with any great degree of certainty. Reports of humans exposed to single massive doses of alkylmercurials are not available. Most cases of poisoning involve ingestion of methyl mercury-contaminated fish or grains treated with either ethyl or methyl mercury fungicides. In such cases mercury is accumulated over a period of time. Secondly, neurological symptoms of methyl mercury poisoning may not occur until weeks or months after the initial exposure (Task Group on Metal Toxicity, 1976; Kurland, 1973). Thus, it is very difficult to estimate fatal doses.

Intake in fatal cases was usually estimated from organ concentrations of mercury. Magos et al. (1976) reported an average liver concentration of 16.3 mg/kg ww in 50 autopsy samples. This concentration, however, was not considered likely to result in death through liver failure. Bakir et al. (1973) estimated body burdens of mercury in patients from plots of the cumulative dose of mercury from ingestion of contaminated bread versus measured blood concentration of mercury. The probability of a fatal outcome was increased at a body burden of 4 mg/kg Hg. The Task Group on Metal Toxicity (1976) estimated that this would correspond to a brain concentration of 17 mg/kg. They also summarized data from previous outbreaks of methyl mercury poisoning and concluded that the minimum lethal level in the brain probably lies between 6 and 17 mg/kg. Using the above figures and assuming complete absorption of methyl mercury, the minimum lethal dose for a 70 kg person would range from ~20-60 mg/kg. This is quite close to lethal levels for inorganic mercury.

Symptoms are dominated by neurological disturbances, although in the case of ethyl mercury, renal effects are also seen (Jalili and Abbasi, 1961). Some of the more severe effects of methyl mercury include blindness, deafness, impaired level of consciousness and convulsions.

Aryl and Alkoxyalkyl Mercurials. The lethal levels of these compounds are not known for humans, but generally fall in the range of 10-40 mg/kg bw for animals (Goldwater, 1973). In one case ingestion of 100 mg of a phenyl mercury compound resulted in only slight GI symptoms. In another case, renal biopsies were normal after ingestion of as much as 1250 mg Hg as phenyl mercury (Task Group on Metal Toxicity, 1976). In general there seems to be no difference in the toxicity of various phenyl mercurials that have been studied. The symptoms (where noted) resembled those of inorganic mercury, probably because of rapid removal of the phenyl group (Ladd et al., 1964).

No reports of acute toxicity of alkoxyalkyl mercurials have been published to date. No toxic effects could be detected in workers preparing and packaging methoxyethyl mercury chloride (Goldwater, 1973). Since these compounds are closely related to mercury diuretics they might be expected to have a low order of toxicity because of ready liberation and excretion of mercury (Baer and Beyer, 1966).

Kidney Effects

Inorganic Mercury Compounds. Clinical manifestations of oral intake of inorganic mercury salts include gastroenteritis with abdominal pain, nausea, vomiting and severe renal disorders leading to anuria and uremia in some cases (Task Group on Metal Toxicity, 1976). In an acute poisoning case reported by Pesce et al. (1977), kidney function was studied following ingestion of about 1.5 g $HgCl_2$. The most dramatic effect was an increase in urinary protein secretion which reached a peak of 6.2 g/day during the first day, then decreased to a normal value of <200 mg/day by day 7. Up to 69% of the protein was a B_2 microglobulin. Since only about 0.37 mg/day of this protein is normally excreted, about 1/300 of the total filtered load, the large amount found in the urine reflects an impairment of tubular function.

Long-term exposure to mercuric salts alone is uncommon in humans. Occupational exposure to mercuric nitrate very likely occurred in the felt hat industry (Neal et al., 1937). However, poisoning may have been due mainly to mercury vapor produced from the mercuric nitrate during the procedure of treating the felt rather than to the mercury salt itself. Kazantzis et al. (1962) performed renal biopsies in two cases of workers exposed to mercuric oxides, mercuric acetate and probably mercury vapors for 4 months and 2 years, respectively. Exposure levels were not stated but urinary concentrations of mercury ranged from 1-1.5 mg/ℓ during exposure. The workers had high urinary losses of protein, hyaline casts in urinary sediments and normal glomerular filtration rates. Renal biopsy showed an abundance of lipids and vacuolization in the epithelium of the proximal tubules. No abnormalities were seen in the glomeruli. Renal concentrations of mercury ranged between 10 and 20 mg/kg fresh tissue.

Kazantzis et al. (1962) felt that the nephrotic syndrome may have been an ideosyncratic reaction since many other workers have similarly high levels of urine mercury without developing proteinuria. This conclusion was strengthened by work on rats indicating a genetic (strain) susceptibility (Druet et al., 1978).

Methyl and Short-Chain Alkyl Mercurials. While severe outbreaks of methyl mercury poisoning caused by ingestion of mercury-contaminated fish or fungicide-treated grain have occurred, the great majority of the symptoms reported involved the nervous system; other organs were seldom mentioned (Katsuna, 1968; Tsubaki et al., 1978; Bakir et al., 1973; Al-Sharistani et al., 1976). While kidney damage does occur at high exposure levels, these effects are overshadowed by the severe nervous system damage as described by Rustam et al. (1975) in a later section.

Jalili and Abbasi (1961) reported on an outbreak of mercury poisoning by an ethyl mercury fungicide. While the nervous system, as with the methyl mercurials, appeared to be most severely affected, polyuria or polydypsia along with albumin in the urine was noted. Although the changes in kidney function were generally noted only in more severe cases of poisoning, it nevertheless appears that ethyl mercury is more damaging to the kidneys than the methyl compounds.

Aryl and Alkoxyalkyl Mercurials. In spite of rather extensive use of phenyl mercury compounds industrially, reports of their toxic effects are rare. Goldwater (1964) found no evidence of toxicity in 13 workers employed for 11-23 years in the manufacture of phenyl mercury. Exposure levels were not reported, but mean urinary concentrations of Hg varied from 0.13-1.60 mg/ℓ among workers.

Methoxyethyl mercuric compounds have come to replace methyl mercury compounds as fungicides because of their lower toxicity. Instances of poisoning by these compounds are rare. Task Group on Metal Toxicity (1976) reported a few cases of kidney damage, albuminuria and occasionally a nephrotic syndrome, but no details of the exposure conditions were given. The symptoms were probably due to the action of inorganic mercury resulting from degradation of the methoxyethyl mercuric radical in the body. Goldwater (1964) found no evidence for toxic effects in 7 workers engaged for 2 months in packaging methoxyethyl mercuric chloride. Urine levels varied from 0.015-1.20 mg Hg/ℓ and blood levels from 0.34-1.09 mg Hg/ℓ.

Nervous System Effects

Inorganic Mercury Compounds. There is limited evidence indicating that exposure to Hg^{++} compounds results in nervous system effects (Barber, 1978; Cheek, 1980). Barber (1978) reported neurological changes in two workers exposed in a mercuric oxide manufacturing plant. While Cheek (1980) reported that a small percentage of children exposed to salts of inorganic mercury developed acrodynia, this lack of extensive findings is likely due to the inability of these compounds to penetrate the blood-brain barrier to any important degree (Jugo, 1976) and to the findings that mercury salts are rapidly accumulated in the kidneys (Rothstein and Hayes, 1960). One cannot exclude a causative role of Hg^{++} in the nervous disorders in workers in the felt hat industry where mercury nitrate was used. As pointed out previously, inhalation of mercury vapor may also have been the cause.

Methyl and Ethyl Mercurials.

Toxicologic Effects -- The toxic effects of methyl mercury have been described in several reviews (Swedish Expert Group, 1971; Nelson et al., 1971; WHO, 1972, 1976; Friberg and Vostal, 1972; Miller and Clarkson, 1973; Task Group on Metal Toxicity, 1976; NAS, 1978). The effects of ethyl mercury have been described by Jalili and Abbasi (1961). The great majority of exposures have involved ingestion of mercury fungicide-treated grain, meat from animals fed contaminated grain and fish from contaminated water.

The first recorded poisoning was in 1863 (Edwards, 1865) when three young laboratory workers developed neurological symptoms 3 months after they were first exposed; two of them died. They were preparing diethyl mercury, but it was likely that the primary exposure was mercury vapor. Hunter et al. (1940) described four cases of methyl mercury poisoning. The patients had worked in a factory that manufactured methyl mercury compounds for use as a seed grain fungicide. They were asymptomatic during the initial 3-4 months of exposure and then symptoms were noted that were confined to the nervous system including paresthesia of the extremities, impaired peripheral field of vision, slurred speech, and unsteadiness of gait and limbs. Examination showed that all four patients had ataxia, constriction of visual fields, and impaired stereognosis, two-point discrimination, and joint position sensation in the fingers; three had dysarthria. In all cases, the maximum severity of symptoms occurred several weeks after exposure to the poison had ceased. The degree of improvement varied, and persisting neurological signs such as ataxia, constriction of the visual field and difficult speech were found in all four cases even after 2-3 years. Twelve coworkers remained asymptomatic. One of the patients died in 1952 and the neuropathological findings were reported by Hunter and Russell (1954). These authors correlated the ataxia with cerebellar atrophy that particularly affected the granule cell layer, and related the visual signs to focal atrophy of the calcarine cortex.

In 1956, four patients who were admitted to the hospital near a factory in Minamata, Japan, exhibited a neurological disorder of unknown etiology. Within a few weeks about 30 individuals with similar complaints were identified in the Minamata area. Faculty from Kumamoto University investigated and by 1959 it became clear that Minamata disease was the Hunter-Russell syndrome of methyl mercury poisoning (Katsuna, 1968), which resulted from the consumption of methyl mercury-contaminated fish from Minamata Bay. The methyl mercury was discharged into the bay from the local factory effluent, but may also have been produced by biomethylation of Hg^{++} released from the factory. Elevated concentrations of methyl mercury were observed in the hair and brains of victims. Similar cases appeared in Niigata, Japan, in 1965; the total number of Japanese cases was reported to be at least 1224 (Tsubaki and Irukayama, 1977). A poison that had previously been recognized as an occupational hazard had become identified as an environmental risk to public health.

In August 1969 a family in New Mexico began to eat pork from a hog that had been fed methyl mercury-treated seed grain (Snyder, 1971; Pierce et al., 1972). Several members of the family suffered severe methyl mercury poisoning. This was the first report of methyl mercury toxicity from eating contaminated meat.

In the winter of 1971-1972 the largest epidemic of mercury poisoning ever recorded occurred in Iraq resulting in the admission of over 6000 patients to hospitals and over 500 deaths (Bakir et al., 1973). The epidemic was caused by eating contaminated bread prepared from wheat and other cereals treated with a methyl mercury fungicide. Quantitative studies relating to this exposure in which hair to blood concentration ratios were calculated, maternal blood and hair concentration as an estimate of fetal exposure was measured, and blood concentration in relation to loaves of contaminated bread consumed have been reported (Bakir et al., 1973; Kazantzis et al., 1976; Mufti et al., 1976; Al-Shahristani et al., 1976; Marsh et al., 1977, 1980).

The symptoms associated with exposure to methyl and ethyl mercurials described by Rustam et al. (1975) were similar to those reported previously for methyl mercury intoxication. Patients reported paresthesia, ataxia in the form of staggering, falling and inability to stand or sit. Dysarthria was reported as slow speech, slurred speech or explosive speech. Visual problems included hazy and foggy vision or an inability to see close objects; hearing loss also occurred. The severely poisoned often became violent. They were reported to have urinary and fecal incontinence, periods of spasticity and jerking movements of the limbs, head or shoulders, bouts of crying, groaning, moaning or shouting. They lay in bed in the fetal position with the lower limbs crossed. Less frequent were symptoms of dizziness, hypersalivation, lacrimation, nausea, vomiting, diarrhea and constipation.

Neurological signs reported consisted of intermittent interference with sensory pathways, drooping of the eyelids, sluggish pupillary reflexes, myoclonic movements, hyperflexia, mixed tendon reflexes, Babinski sign and one case of decerebrate rigidity.

The previously described exposures have generally involved exposure to methyl mercury compounds, although during the 1971-1972 Iraqi episode small amounts of ethyl mercurials were also present (Al-Damluji et al., 1976). Before the 1971-1972 outbreak many cases of mercury poisoning occurred in Iraq as a result of eating grain treated with ethyl mercury p-tolulene sulphonamide. The primary effects as described by Jalili and Abbasi (1961) were similar to those with methyl mercury poisoning. The report, however, indicated greater involvement of other organ systems in addition to the nervous system with GI symptoms such as vomiting and diarrhea, decreased rate or irregular heartbeat, skin lesions and altered kidney functions. These other symptoms, however, were generally not severe and nervous system effects still predominated.

Dose Response Relationships -- An exhaustive review of toxicological and epidemiological data regarding methyl mercury poisoning in man and animals was conducted by a Swedish Expert Group (1971) in the late 1960's. This review was initiated because of the discovery that widespread mercury pollution existed in Swedish lakes and rivers, that all forms of mercury were subject to biomethylation by microorganisms present in sediments in both fresh and oceanic water, and that fish readily accumulated and concentrated methyl mercury in their edible tissues. The main effort of this group was to determine the margin of safety in the Swedish population with respect to dietary intake and risk of poisoning from methyl mercury in fish by obtaining information on relationships between the following: 1) blood concentrations and risk of methyl mercury poisoning (frequency of signs and symptoms), and 2) long-term dietary intake and steady-state blood concentrations. By combining these two relationships they obtained estimates of risks to various groups in the Swedish populations classified according to their fish consumption. Ultimately this information was used by the Swedish government to set regulations on maximal permissible concentrations of methyl mercury in fish.

The Swedish group had to rely on limited data from the Niigata outbreak for information on blood concentrations and health effects. Blood samples had been collected from only 17 patients (Figure VI-1); these data were insufficient to establish a statistical relationship between blood concentration and frequency of poisoning cases (blood concentration-response). Consequently, they attempted to identify the lowest blood concentration associated with the onset of signs and symptoms of poisoning. In patients from whom several blood samples had been collected, the methyl mercury concentration fell exponentially with time, corresponding to a half-time of ~70 days. Where sufficient data points were available, the blood concentration was extrapolated back to the time of onset of symptoms. The group concluded that the lowest concentration in blood associated with the onset of symptoms in the most sensitive individual was 0.20 mg Hg/ℓ whole blood. Using a safety factor of 10, they calculated the maximum safe blood concentration to be 0.02 mg Hg/ℓ. This safety factor was applied in consideration of the greater sensitivity of the fetus, as compared with adults.

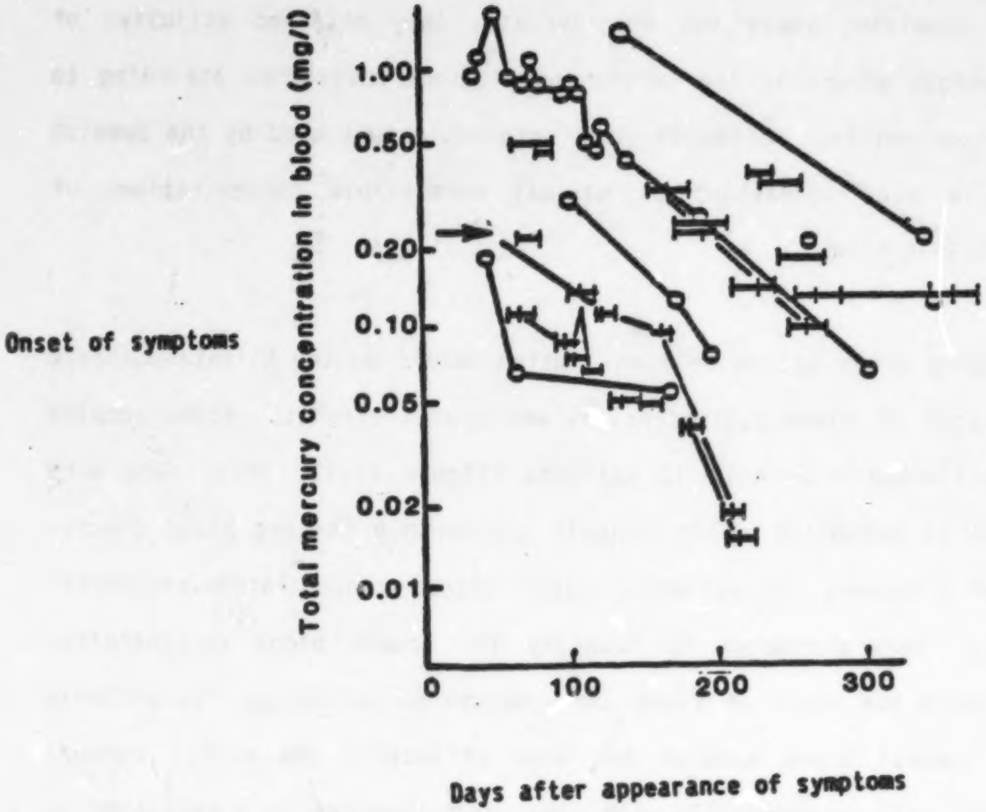

FIGURE VI-1

Concentration of mercury in samples of blood collected from patients suffering from methyl mercury poisoning in the Niigata outbreak. Samples from the same patients are connected by a straight line. The arrow indicates the estimated blood level for onset of symptoms. The units of mercury concentration in blood are µg Hg/100 mℓ. The numbers on the ordinate should be divided by 100 to convert to mg Hg/ℓ.

Source: Swedish Expert Group, 1971

From studies of Swedish fishermen and their families whose regular diet contained fish, the Swedish Expert Group (1971) concluded that an average daily intake of 0.30 mg Hg as methyl mercury would yield a steady-state blood concentration of 0.20 mg Hg/ℓ and that the maximum safe daily intake would be 0.03 μg Hg. WHO (1972) endorsed these conclusions by recommending a tolerable weekly intake arithmetically equivalent to the Swedish maximum safe daily intake.

The Swedish Expert Group (1971) review contains several weaknesses and uncertainties. For example, the accuracy of the analytical methods used to detect mercury during the Niigata outbreak is uncertain. It was necessary to extrapolate the observed blood concentrations back to the time of onset of symptoms, with a resulting high degree of statistical uncertainty in the linear extrapolation. The Swedish data relating dietary intake to blood concentration are also fraught with uncertainty. By the time more recent reviews were published in 1976 and later, several studies had been completed on fish eating populations and reports had appeared on the large outbreak of poisoning in Iraq.

Clarkson et al. (1975, 1976) compared the frequency of paresthesia with mercury concentrations in blood (Figure VI-2) using data from the Iraqi outbreak reported by Bakir et al. (1973). Frequencies of paresthesia (5-10%) observed at low Hg concentrations were interpreted to be background values for the population and unrelated to methyl mercury. The point of intersection of the two lines representing paresthesia frequencies and Hg concentrations was taken to indicate the blood Hg concentration (0.29 mg Hg/ℓ) at which paresthesias caused by methyl mercury emerge above the background

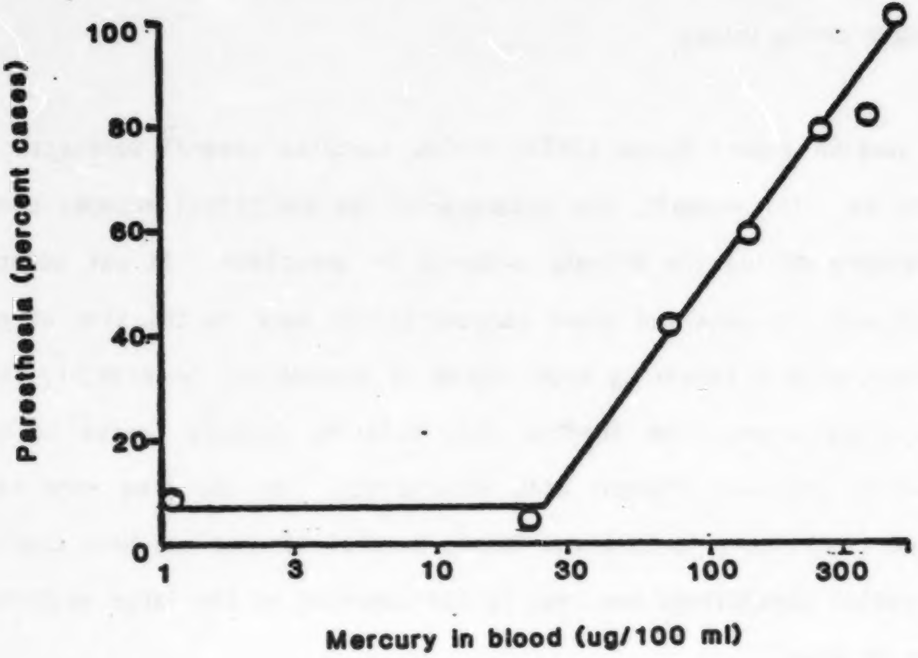

FIGURE VI-2

The frequency of paresthesia as a function of the concentration of mercury in blood 65 days after cessation of exposure. The graph uses data from Table 4 of Bakir et al. (1973). The mean blood concentrations are computed as the logarithmic means for each cohort in their table. The line connecting the first two points was assumed to be horizontal. The line connecting the other points was computed by least squares linear regression analysis.

Source: Clarkson et al., 1976

frequency. However, the Hg concentrations were those existing 65 days after cessation of exposure to methyl mercury and, in view of the reported blood Hg half-life of 65 days in these patients, the maximum blood Hg concentration was probably about 0.48 mg Hg/ℓ whole blood at the end of exposure.

Al-Shahristani et al. (1976) reported no cases of methyl mercury poisoning occurring at a concentration of <120 mg/kg hair, equivalent to ~0.48 mg Hg/ℓ whole blood. WHO (1976) estimated total dose according to the amount of contaminated bread consumed. The background parasthesia frequency was estimated to be about 4%, and the total body burden of methyl mercury at which paresthesias caused by methyl mercury emerged above the background frequency was ~37 mg. Since the average body weight in the group was 50 kg, this dose would correspond to ~50 mg in a 70 kg human. The equivalent blood concentration would be ~0.50 mg Hg/ℓ whole blood based on the assumption that 1 ℓ of blood contained 1% of the total body burden of Hg. These results are in general agreement with those reported by Marsh et al. (1980) (Figure VI-3). If hair concentration averages 300 times blood concentration, then effects were noted at blood levels of 0.33 mg/ℓ or greater.

The Iraqi studies failed to identify a diagnosed case of methyl mercury poisoning at 0.20 mg Hg/ℓ whole blood. If such cases existed, they could not be differentiated from individuals having nonspecific signs and symptoms. The Iraqi studies clearly show a need for more specific tests for effects of methyl mercury at low doses.

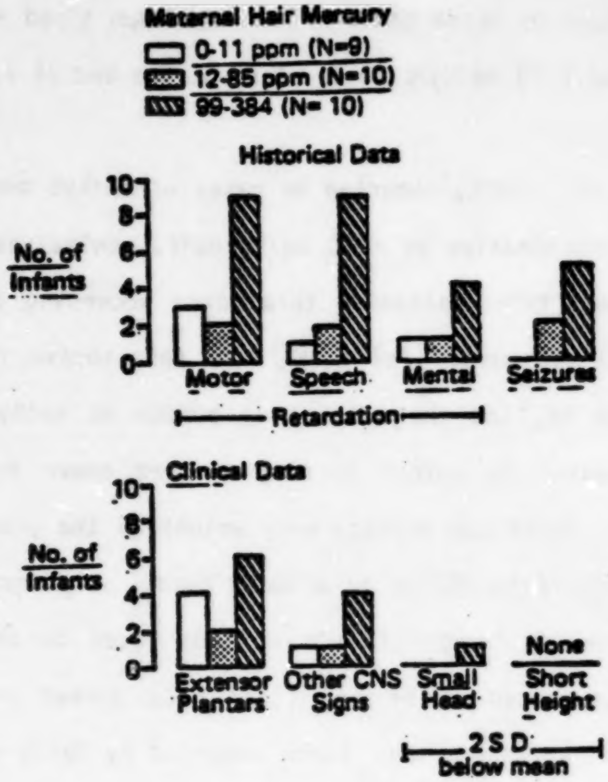

FIGURE VI-3

Signs (clinical data) and symptoms of psychomotor retardation in 29 Iraqi infants exposed prenatally to methyl mercury. The frequency of abnormalities are compared in groups of infants according to the maximum maternal hair concentration during pregnancy.

The following criteria for abnormalities were adopted: motor retardation if the child was not walking at 18 months, speech retardation if not talking by 24 months, mental retardation or seizures (or convulsive-like attacks) according to the history provided by the mother, and neurological signs by agreement of the two examiners. No standards are available for head circumference or height of Iraqi children, so these factors were evaluated in terms of standard deviations below the mean for the group.

Source: Marsh et al., 1980

WHO (1976) also reviewed several studies of fish-eating populations. Findings in Peru (Turner et al., 1974) and Samoa (Marsh et al., 1977) agreed with those from other fish-eating populations. No adverse health effects in adults could be associated with exposure to methyl mercury from fish. However, only about 15 people had blood levels in the range of 0.20-0.40 mg Hg/ℓ.

Since the WHO (1976) review, reports have been done on Canadian Indians exposed to methyl mercury from contaminated fish (Clarkson et al., 1975; Wheatley et al., 1979; Phelps et al., 1980). One or more blood samples were analyzed from 379 residents of two Ojibway Indian Reserves in northwestern Ontario, and at least one hair sample was taken from each of 945 residents. The ratio of total hair to blood mercury concentration averaged ~300 (Phelps et al., 1980). Repeated sampling of one resident also produced numbers in good agreement with this ratio. Blood levels of total mercury ranged from 0.005-0.33 mg Hg/ℓ, most of which was in the form of methyl mercury.

A Japanese team conducted clinical examinations on 89 of the 1200 residents of the two reserves (Harada et al., 1976). A variety of sensory, coordination and other neurological disturbances were found (paresthesia, visual field constriction, ataxia, dysarthria) similar to those reported in cases of methyl mercury poisoning in Japan. However, as the authors pointed out, the neurological symptoms were relatively mild and many were thought to be due to other causes.

A Canadian medical team examined 49 Cree Indians living in northwestern Quebec who were exposed to methyl mercury in fish. They concluded that at least 6 and possibly 25 people showed signs of methyl mercury intoxication (Barbeau et al., 1976). The blood levels of mercury were elevated with 80% having levels >0.05 mg Hg/ℓ. The lack of appropriate controls for such confounding factors as age, alcohol intake and nutrition makes it impossible to draw conclusions on the role of methyl mercury in the clinical picture of both the Harada and Barbeau investigations.

More accurate analysis of blood levels reported on the Niigata outbreak by Tsubaki et al. (1978) suggested that the Swedish Expert Group had overestimated the risk and evidence for a lowest-observed-effect level (LOEL) of 0.20 mg Hg/ℓ blood. More recent information, however, indicates that the risk had not been overestimated. For example, Tsubaki et al. (1978) also presented data on four patients described as having methyl mercury poisoning with delayed onset. The maximum hair concentration in the four patients ranged from 50-300 mg Hg/kg indicating blood concentrations as low as 0.166 mg Hg/ℓ. Data on monkeys by Evans et al. (1977) showed that the onset of symptoms is inversely related to blood concentration and may be delayed a year or more. Rice and Gilbert (1982) detected symptoms in monkeys having blood concentrations ranging from 0.60-0.90 mg Hg/ℓ, indicating the NOEL was below this range of blood levels. Finally, the continuing studies on Canadian Indians suggests effects may occur at blood concentrations near 0.20 mg Hg/ℓ (Methyl Mercury Study Group, 1980). Based on the above evidence it would be prudent to retain the 0.20 mg Hg/ℓ as the LOEL in nonpregnant adults. This is in agreement with a WHO expert group (1980) that concluded a low prevalence (~5%) of the population should expect the earliest symptom (paresthesia) at blood concentrations of mercury in the range of 0.20-0.50 mg/ℓ.

Aryl and Alkoxyalkyl Mercurials. The toxicology of phenyl mercurial compounds in humans was reviewed by Ladd et al. (1964). The occurrence of poisoning was extremely rare and nervous system effects were not reported. In the case of alkoxyalkyl mercurials, no nervous system effects were likewise noted (Goldwater, 1973). More recently Astolfi and Gotelli (1981) did report the development of acrodynea in a few of an estimated 6000 infants exposed to phenyl mercury compounds. According to Merville et al. (1967), the patterns of accumulation in the kidneys and elimination was similar for phenyl mercuric acetate and methoxyethyl mercuric chloride. The rapid accumulation in the kidneys indicates that the renal system, rather than the nervous system, would be expected to be the primary target organ for these compounds.

Effects of Prenatal Exposure

Inorganic Mercury Compounds. Studies relating to the effects on humans of prenatal exposure to mercuric salts have not been found in the available literature.

Methyl and Short-Chain Alkyl Mercurials. Engleson and Herner (1952) were the first to report on psychomotor retardation resulting from fetal exposure to methyl mercury. A Swedish family had eaten porridge made with methyl mercury-treated grain. The asymptomatic mother gave birth to a daughter who appeared to be normal at birth and in the first 2 months of life. It later became clear that the child was both mentally and physically retarded. Upon examination a year or two later, she continued to have marked psychomotor retardation, and the authors postulated that "mercury intoxication, perhaps during early fetal life, seems to us to be a possible cause." Her father and brother were also diagnosed as having neurological symptoms of mercury poisoning. Urinary mercury concentrations were elevated in the mother; no blood or hair analyses were performed.

Harada (1968) reported on 22 children from Minamata, Japan, who had severe psychomotor retardation which he concluded was due to fetal methyl mercury poisoning. All children came from families in which at least one other member had been diagnosed as having methyl mercury poisoning, with fatal results in 13 families. Five of the mothers had experienced transient paresthesia during pregnancy but otherwise had been in good health. The childrens' ages ranged from 1-6 years at the time of initial examination; at those ages it was not possible to determine their degree of exposure to methyl mercury in utero. Two of these children died and neuropathological studies were reported by Takeuchi (1968) who concluded there was evidence of a disturbed brain development with the presence of cerebral and cerebellar lesions.

In August 1969, a family in New Mexico began to eat pork from a hog that had been fed methyl mercury-treated seed grain (Snyder 1971; Pierce et al., 1972). At that time the mother was 3 months pregnant and ate the contaminated pork regularly for the following 3 months. She remained asymptomatic but delivered a severely brain-damaged infant who, at 8 months of age, was blind and hypotonic. Some other members of the family suffered severe methyl mercury poisoning. This was the first report of methyl mercury toxicity from eating contaminated meat in the United States and the only published case involving fetal exposure in this country (Snyder, 1971).

The Iraqi outbreak offered an excellent opportunity to develop quantitative information with regard to prenatal exposures to methyl mercury. Large numbers of people, of both sexes, were exposed to a wide range of dietary intake of methyl mercury within a period of a few months. More than 6000 residents were hospitalized with clinical signs of methyl mercury poisoning, but many exposed individuals were not hospitalized. Pregnant females could have been exposed to a pulsed dose of methyl mercury at any time during pregnancy and may have consumed a wide range of doses. Early studies on 15 mother-infant pairs identified infants who were prenatally exposed to and severely poisoned by methyl mercury (Amin-Zaki et al., 1974a). Choi et al. (1977, 1978) reported abnormal neuronal migration in a human infant who was prenatally poisoned with methyl mercury in Iraq. A group of infants was also identified that had been exposed to methyl mercury primarily by nursing (Amin-Zaki et al., 1974b).

A University of Rochester team obtained dose-effect relationships between prenatal exposure and effects on the infants in follow-up neurological and pediatric studies (Marsh et al., 1977, 1980). Nine infants from mothers who had maximum hair concentrations in the range of 0-11 ppm and 10 in the range of 12-85 ppm did not differ significantly in signs and symptoms of motor retardation. Ten infants of mothers who had maximum hair concentrations in the range of 99-384 ppm (mg/kg) had significantly greater incidences of motor retardation $p<0.01$, speech retardation $p<0.001$, and seizures $p<0.03$ than the infants in the two lower groups, which were combined into one group of 19 for statistical purposes (see Figure VI-3). The high mercury group also differed from the other two groups in the number of infants having multiple signs and in the number of poisoning symptoms

($p<0.005$, Fischer exact test). For example, 8 of 10 infants in the high exposure group had three or more adverse health effects per infant. In contrast, in the two groups with lower exposures the infants had one or no adverse effects.

In a more recent report on the mercury-intoxicated Iraqi population (Marsh et al., 1981) 84 mothers and their children were studied. The study group included a wide spectrum of exposures. Data on paired groups of 14 mothers and children at each of six different ranges of maternal hair peak mercury concentrations were analyzed. The frequency of neurological symptoms in children is shown in Table VI-1. Symptoms increased in parallel with exposure. Symptoms in the mothers (most frequently paresthesia) also increased in parallel to exposure, but maternal symptoms were mild and transient. The children were examined by two independent teams of neurologists. Five of 14 children had severe psychomotor retardation; the corresponding maternal hair peak mercury levels ranged between 165 and 320 mg Hg/kg. Moderate signs appeared in 3 of 14 children at a maternal peak hair concentration of 37 mg Hg/kg (range 18-67.6 mg Hg/kg).

Most of the children were exposed only during part of gestation. For example, 8 of 28 with peak maternal hair mercury levels in this range were exposed either in early or late stages of pregnancy. The most severely affected children had been exposed to methyl mercury during the second trimester of pregnancy. Furthermore, 4 of 28 children whose mothers had peak hair mercury levels of 10-67.6 mg Hg/kg were exposed to concentrations lower than the peak maternal concentration (i.e., the maternal peak hair mercury concentrations did not correspond with the time of pregnancy).

TABLE VI-1

Frequency of Symptoms of Mothers and Children Related to Maternal Hair Peak Hg During Pregnancy*

Maternal Hg Hair Levels			Symptoms					
			Maternal: Neurological Symptoms	Child: Retarded			Seizures	Total Number of Symptoms of Children
Peak Range (ppm)	Mean (ppm)	N		Walk	Talk	Mental		
0.4-6.0	3	14	1	2	1	1	0	4
6.1-10.0	8	14	2	4	1	0	0	5
10.0-18.0	13	14	1	0	0	0	0	0
18.0-67.6	37	14	5	5	7	2	2	16
68.0-180	125	14	7	6	5	3	3	17
204-640	293	14	6	9	6	3	3	21

*Source: Marsh et al., 1981

It must be emphasized that in this study exposure was subacute not chronic, thus these data cannot be extrapolated to effects of constant levels of exposure during pregnancy.

Although brain damage caused by prenatal exposure to methyl mercury has been shown in these preceding studies, no anatomical defects have been reported in humans except for abnormal cytoarchitecture of the brain in prenatally exposed infants (Choi et al., 1978). However, adequate epidemiological studies have not been performed and the possibility of teratologenic action by methyl mercury in humans cannot be ruled out.

Phenyl and Alkoxyalkyl Mercurials. No information is available in the published literature relating to the effects of exposure to these compounds prenatally upon subsequent development in humans.

Mutagenicity

No evidence has been presented to date for the mutagenicity of mercuric salts, phenyl or alkoxyalkyl mercury compounds. While no direct mutagenic effects of methyl mercury have been reported in humans, a statistical relationship was found between the frequency of chromosome breaks and blood concentration of methyl mercury in 23 Swedish subjects on fish diets. The Hg concentration in the blood of the exposed group ranged from 0.014-0.116 mg Hg/ℓ and 0.003-0.018 mg Hg/ℓ in the nonexposed subjects (Skerfving et al., 1974). In a study conducted a few months after the Iraq outbreak, however, no correlation between chromosomal damage and exposure to methyl mercury could be detected (Farman, 1974).

Carcinogenicity

No evidence could be located in the available literature that links mercury exposure to cancer in humans.

Summary

Most reports regarding exposure to mercuric salts have been related to acute exposure, either accidental or as a result of attempted suicide. The primary effects reported were erosion of the intestinal tract and kidney damage. The effects of long-chain alkyl mercurials is generally similar to that of the inorganic salts because of rapid cleavage of the organic moiety.

Toxic effects of methyl mercury have usually occurred as a result of ingestion of fungicide contaminated grain or mercury contaminated seafood. The primary symptoms are neurological. Detectable effects that are due to methyl mercury exposure have been shown to occur at blood concentrations as low as 200-600 ng/mℓ and death is associated with a body burden of 4-6 mg/kg (Clarkson et al., 1975).

Fetal effects occur at a lower blood concentration of mercury than those causing maternal effects. There is little evidence for either mutagenic or carcinogenic effects of mercury in humans.

VII. MECHANISMS OF TOXICITY

In this section more general theories of the mechanisms of action of mercury as well as the more specific theories relating to target organs, cells and enzyme systems are discussed. In addition, the action of mercury upon the mature as well as the developing nervous system is covered.

General Theories on Mechanisms

Affinity for Sulfhydryl Groups. It has been believed for a number of years that the fundamental biologic activity of mercury was related to the strong affinity of ionic mercury for sulfhydryl or thiol groups (Hughes, 1957; Passow et al., 1961; Peters, 1963). This belief was strengthened by the findings of Clarkson (1972b) that, not only did mercury have a strong affinity for thiol groups in proteins and other biological molecules, but that this affinity was far in excess of its affinity for other biologically occurring ligands.

Despite this knowledge it has proven difficult to pinpoint the specific locus of activity for mercury. Nearly all proteins contain sulfhydryl groups. Furthermore, because most sulfhydryl groups are important in most protein functions, mercury can disturb almost all functions in which proteins are involved. Thus, almost every protein in the body is a potential target organ and mercury may inflict cellular damage where it is present in sufficient concentration.

As pointed out by Rothstein (1973) almost all mercury compounds will react with sulfhydryl groups. In organomercurials such as the alkyl, alkoxy and aryl series, although the carbon-mercury bond is nonionic (covalent) and of varying stability in biological systems, the mercury atom still retains a free valency electron, i.e., the mercury or other anion bond is ionic. Organomercury salts ionize to form monovalent cations (Ostlund, 1969). Nonionic elemental mercury vapor passes through the lipid rich cell membranes unimpeded by electric charge or binding to large molecules. Once inside cells, it becomes oxidized to the ionic form which then binds to intracellular proteins and can only leave the cell with difficulty (Clarkson, 1972a).

It is generally agreed that mercury binds to sulfhydyl groups. These groups however, are present throughout the cell and reaction with them can affect may cell processes. Attempts to define more specifically the action of mercury led to the proposal of several concepts.

Cell Membranes. Passow et al. (1961) from in vitro experiments on isolated cells and tissues claimed that the cell membrane was the first site of attack by heavy metals. This concept seemed reasonable topographically due to the fact that the cell membrane is known to contain sulfhydryl groups. Although Passow et al. (1961) summarized many studies to support his claim none of them were carried out in vivo so the role of membrane damage in the pathogenesis of heavy metal poisoning still remains to be established.

Intracellular Membranes. Other investigators felt that the primary effect of mercury was on intracellular membranes. Verity and Reith (1967) studied the effects of mercury within cells for interference with the integrity of lysozomal membranes that contain essential thiol groups.

Exposure of lysozomal preparations to inorganic and organic mercurials induced an irreverisible damage to the membrane with resulting enzyme activation. The various lysozomal hydrolase preparations reacted differently at constant mercury levels suggesting a different pattern of binding unique for each enzyme studied, which could also explain differing sensitivity of various tissues to mercury. Again, however, the studies were conducted _in vitro_ so final proof was not available.

Concentration Dependency. Since mercury is nonspecific in terms of protein binding it has been suggested that mercury will inflict cellular damage wherever it accumulates in sufficient concentration (Rothstein, 1973). Thus, the relative toxicity of mercury is related to its selective distribution. Studies by Somjen et al. (1973b) on the microdistribution of mercury lend support to this hypothesis in that the spinal root ganglia, important sites of peripheral nerve damage, are also the areas of highest accumulation of methyl mercury in rats. This concept is also supported by the observations that mercury compounds are rapidly accumulated by the kidney, a target organ for the toxic effects of mercury in rats (Rothstein and Hayes, 1960). Distribution factors, however, can only partially explain the toxicity of methyl mercury, since, in most species the brain is more sensitive despite the fact that the greatest accumulation occurs in the kidney (WHO, 1976).

Mechanisms of Action on Specific Organ Systems

Autoimmune Mechanisms in the Renal System. More recent attempts to elucidate mechanisms of action have focused on specific target organs, often with the goal of determining effects of mercury upon enzyme systems.

Studies relating to the pathological effects of mercury on the renal system suggested the operation of an immune type of mechanism. For example, in one strain of rat it has been possible to induce an autoimmune glomerular nephritis by treatment with $HgCl_2$ (Druet et al., 1978). As a result of this finding it was hypothesized that immunoglobulin deposition contributes to the glomerular dysfunction found in workers exposed to mercury vapor (Buchet et al., 1980). Tubbs et al. (1982) listed the following possible mechanisms to account for immunopathologic findings in mercury nephropathy: 1) mercury may combine with a serum protein and antibodies are formed against the hapten; 2) antirenal tubular epithelial cell or antinuclear antibody formations may be involved; 3) mercury induces antibodies to basement membrane and extracellular collagen matrix and a mesangiopathic proliferative glomerulonephritis develops as immune complexes are formed in the glomerular basement membrane.

Vasoconstrictive Action in the Renal Vasculature. One of the better understood actions of mercury is its vasoconstrictive effect in the kidney. Solomon and Hollenburg (1975), working with the renal vasculature of the dog were the first to show that catecholamine release was the mechanism of Hg-induced vascular smooth muscle contraction. Although the precise manner in which the catecholamine was released was not determined by these investigators, a probable mechanism is the inhibition of monoamine oxidase (MAO) an -SH dependent enzyme that metabolizes and inactivates the catecholamine serotonin (5-hydroxytryptamine). Serotonin is a vasoconstrictive amine (Magistretti and Peirone, 1961). As Solomon and Hollenberg (1975) found, the contractile response to serotonin was unimpaired in the presence of Hg^{+2}. MAO inhibition would thus appear to be a reasonable mechanisms of catecholamine release.

Central Nervous System. The nervous system has been studied extensively since it is a primary target organ for both nonionic mercury as well as alkyl mercury compounds. For recent reviews of the mechanism of action of methyl mercury on the nervous system see Mottet and Ferm (1983) and Rodier (1983). Both forms penetrate the blood brain barrier quite easily as compared with inorganic mercury salts (Jogo, 1976) that penetrate the brain poorly and are accumulated primarily in the kidney. Despite the fact that alkyl mercury compounds are rapidly distributed to all parts of the body, (Charbonneau et al., 1976) brain damage is not immediately evident. Bakir et al. (1973) reported a silent period that varied from weeks to months in which there were no neurological symptoms in exposed humans. Any acceptable theory explaining mechanisms must take into account this silent period that is discussed in more detail further on.

One explanation for the toxic effects of mercury in the brain arose from the discovery by Yoshino et al. (1966) and subsquently confirmed by others Cavanaugh and Chen, 1971b; Verity et al., 1977; Omata et al., 1978, 1980a) that methyl mercury inhibited protein synthesis in the brain. Syversen (1977) then investigated the effects of methyl mercury on Purkinje and granular cells from the cerebellum as well as neuronal cells from the cerebrum. Both mercury accumulation and inhibition of protein synthesis were roughly equal. Purkinjie and neuronal cells, however, were able to recover from the initial inhibition of protein synthesis and to actually exceed control levels in some cases, indicating that a repair process had occurred. Granulated cells, on the other hand, the cells known to be damaged by the concentration of mercury used, were unable to recover protein synthesis. Thus, in the first phase of the attack, in which symptoms may not be noted (the silent phase), most cells are affected, but permanent damage occurs only in those cells unable to repair the initial insult.

These investigators have pointed out, that a major effect of mercury is related to protein synthesis. Since the damage to cells is apparently not related to an initial inhibition of protein synthesis, but to a later inhibition of repair processes, the findings are in agreement with the presence of a silent period. These studies, however, do not explain how protein synthesis and the repair processes are inhibited, or why some cells were able to repair initial damage while others were not.

Ganther (1978) sought to explain the actions of methyl mercury on the CNS by hypothesizing that the carbon-mercury bond in methyl mercury undergoes cleavage to release methyl free radicals. These, in turn will initiate a chain of events involving peroxidation of lipid constituents of neuronal cells. The silent phase would result from the delay as various systems defend against lipid peroxidation until finally, a rapid progressive degeneration of tissue would occur. This might also explain the protective action of vitamine E and selenium that are involved in the decomposition of peroxides that are cofactors in free radical formation. Omata et al. (1980b) did not detect any significant biotransformation of methyl mercury in the brain up to 15 days after a single exposure. However, since the silent period can last for months, the transformation rate may be very slow and not detected after only 15 days.

Peripheral Nervous System. At high doses, methyl mercury has been shown to affect the peripheral as well as the CNS (Rustam et al., 1975). Patients who had symptoms of CNS damage due to methyl mercury also exhibited muscular weakness. When treated with an acetylcholinesterase inhibitor, neostigmine, their ability to raise heavy weights was greatly increased, thus indicating problems at the neuromuscular junction. Studies with isolated nerve-muscle preparations indicated that a much greater concentration of acetylcholine was needed in the methyl mercury treated preparation to produce the same degree of contraction as the control preparation (Von Burg and Landry, 1976). Further studies (Eldefrawi et al., 1977; Sager et al., 1982) have identified these defects as due to a specific inhibition of the binding of acetylcholine (ACh) to the ACh- receptor. This inhibition of binding was found for methyl mercury but not $HgCl_2$, possibly resulting from a lack of penetration into the cells by inorganic mercury.

Abe et al. (1975) also found that methyl mercury blocks axonal transport of nutrients in a manner similar to colchicine and that methyl mercury has the ability to cause depolymerization of microtubules *in vitro*. Abe et al. (1975) concluded that methyl mercury probably produces axonal blockade by reacting with -SH groups on microtubule proteins. If mercury does indeed react with microtubules *in vivo* the consequences could be profound. Microtubules maintain and modify cellular shape, are involved in axonal transport of nutrients, and through the spindle apparatus, control movements involved in neural migration.

Developing Nervous System. In recent years the effects of mercury on the developing nervous system has attracted increasing attention. Prenatal exposure of humans has resulted in disturbances in the cytoarchitecture of the brain, and brain size is diminished in severe cases (Choi et al., 1978). These authors attributed the pathological findings to incomplete and abnormal migration of neuronal cells to the cerebellar and cerebral cortices.

This conclusion was supported by studies of Choi et al. (1979), showing that methyl mercury inhibited migration and movement of cultured human cells.

Methyl mercury may also inhibit brain development by arresting division of immature neurons at critical stages of brain development. Methyl mercury is known to inhibit cell division by causing metaphase arrest, similar to that observed with mitosis spinal inhibitors such as colchicine, presumably by disruption of the mitotic spindle (Ramel, 1969). To test this hypothesis Sager et al. (1982) administered methyl mercury to newborn mice at a time when the external granular layer of the cerebal cortex was rapidly dividing. They found a decreased number of granular cells in the treated animals as well as a decrease in the percentage of late mitotic figures.

Both deranged cell migration and arrested cell division might be an expression of the action of mercury on microtubules and thus could be consistent with microtubule proteins being an important molecular target for methyl mercury in the developing brain.

Summary

Many, if not all of the toxic effects of mercury compounds can be related to their affinity for -SH groups in proteins and related compounds. Some investigators have attempted to show that the reactions responsible for cellular damage take place at the cell membrane while others showed evidence that the primary reactions occurred on intracellular membranes. The primary target organs were believed by some to be those in which mercury reached the greatest concentration.

Recent renal studies have shown that glomerulonephritis is most likely mediated through an immune mechanism, while vasoconstriction was due to an inhibition of MAO.

Damage to CNS neuronal cells was found to be due to their inability, unlike Purkinje cells, to recover from an initial inhibition of protein synthesis. In the developing nervous system mercury has been shown to block normal growth by causing incomplete or abnormal migration of neurons, while other studies have shown that neuronal division is inhibited at critical stages of development.

In the peripheral nervous system muscular weakness was found to be due to an inhibtion of binding of ACh at the neuromuscular junction, which in turn was likely to be related to a blockage of axonal transport.

Overall, much has been learned about possible mechanisms of toxicity of mercury compounds, but it is still unclear how these substances produce many of the observed biological and biochemical effects.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS guidelines (NRC,

1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify mercury as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is, thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Almost all mercury in uncontaminated drinking water is thought to be in the form of Hg^{++} (U.S. EPA, 1980). Thus, intake of organic mercury compounds, especially the alkylmercurials, are unlikely to pose a direct risk through ingestion of drinking water. But, the possibility of the conversion of methyl mercury to inorganic mercury does exist. Methods to quantitate this conversion are presently not available and therefore are not taken into consideration. The studies evaluated in this section will, therefore stress those relating to the intake of mercury salts. In the development of a criterion, however, the possible additive effects of methyl mercury ingested from aquatic organisms should be considered.

Since mercury in the Hg^{++} form is poorly absorbed through the GI tract [7% in humans (Rahola et al., 1971) and 1-2% in mice (Clarkson, 1971)] and does not penetrate cell membranes rapidly, it is less toxic than methyl mercury. As a result there has been less interest in studying this form of mercury and fewer studies are available, especially concerning human exposure.

In male rats, Miura et al. (1981) found that 0.2 mg/kg Hg administered i.p. as $HgCl_2$ caused kidney damage within 24 hours. Examination with the aid of an electron microscope showed derangement of cellular ultrastructure of the proximal tubules. Kidney accumulation of mercury in this study, however, indicated that absorption was likely to be much greater than by the oral route. In order to extrapolate results to humans, a consideration of absorption efficiencies would be necessary. Lee and Dixon (1975) using the same route of exposure reported that a single 1.0 mg/kg bw dose of mercuric chloride resulted in decreased fertility in male mice.

Short-term and subchronic studies were conducted by Bariety et al. (1971), Druet et al. (1978), Weening et al. (1978) and Makker and Aikawa (1979) in which rats were injected s.c. 3 times weekly with solutions of mercuric chloride for periods of up to 8 months. Dose levels varied from 0.05-2.5 mg/kg bw/injection (0.02-1.07 mg/kg/day). Glomerulonephritis was detected at doses as low as 0.43 mg/kg, proteinurea at 0.04 mg/kg, and antibody production at doses as low as 0.02 mg/kg/day.

These studies were adequately designed and conducted but are not useful for setting standards in drinking water. A definite NOEL for pathological effects in the kidney would have been helpful in three of the four studies. Another criticism of these studies for use in risk assessment was the utilization of the s.c. route of exposure, but this should not be grounds for rejection of these types of studies. Chang and Hartmann (1972a,b), for example, found little difference between the effectiveness of orally administered $HgCl_2$ versus the s.c. route. Gale (1974) also reported similar effectiveness of the two routes in studying the teratogenic effects of Hg acetate, indicating the percentage of mercury absorbed was about the same.

The only chronic ingestion study designed to evaluate the toxicity of mercury salts was reported by Fitzhugh et al. (1950). In this study, rats of both sexes (20-24/group) were given 0.5, 2.5, 10, 40 or 160 ppm mercury as mercury acetate in their food for up to 2 years. Assuming food consumption was equal to 5% bw/day, the daily intake would equal 0.025, 0.125, 0.50, 2.0 and 8.0 mg/kg bw for the five groups, respectively. At the highest dose level a slight depression of body weight was detected in male rats only. The statistical significance of this body weight depression was not stated. Kidney weights were significantly ($p<0.05$) increased at the 2.0 and 8.0 mg/kg bw dose levels. Pathological changes originating in the proximal convoluted tubules of the kidneys were also noted at these dose levels with more severe effects in females than males.

The Fitzhugh et al. (1950) study was criticized by Goldwater (1973). The primary weakness was the small number of animals surviving past 18 months. For example, the increase in kidney weights in the two highest exposure groups was based on only 6 and 7 animals/group. The number of animals in each group having detectable pathological changes was not stated.

Finally, a statistical analysis of body weights, to determine if the decrease in body weight gain among males in the highest exposure group was significant, would have been helpful.

The lethal dose of mercury chloride in man has been estimated to be in the range of 14-57 mg/kg bw (Gleason et al., 1957). Pesce et al. (1977) reported that a young adult male survived an ingestion of 1.5 g (21 mg/kg bw) mercuric chloride, although acute symptoms were severe. No chronic studies are available for man except for the report by Kazantzis et al. (1962) where workers were exposed to several mercury compounds including inorganic mercury compounds. The workers had high urinary losses of protein, hyaline casts in urinary sediments and normal glomerular filtration rates.

Existing Guidelines and Standards

A WHO expert group recommended an international standard for drinking water of 1 μg Hg/ℓ (WHO, 1971, 1984). The U.S. EPA (1980) has recommended a standard for the protection of ambient water quality of 144 ng/ℓ (U.S. EPA, 1980) and for drinking water of 2 μg/ℓ (U.S. EPA, 1973).

Quantification of Noncarcinogenic Effects

1-Day and 10-Day Health Advisories. There are insufficient data to determine 1-day and 10-day HAs for mercury in drinking water.

Animals studies have indicated effect levels of 0.2 mg and 1 mg/kg bw for kidney damage and reproductive effects, respectively. However, these adverse effects were observed when the animals were administered a single i.p. dose of mercuric chloride. It has been shown that absorption by the i.p. route is greater than oral absorption. By the oral route, humans are estimated to absorb 7% of Hg; rats absorb ~1.0%.

Assuming 100% absorption by the i.p. route and 7% by the oral route, the approximate total toxic dose by the oral route would be as follows:

$$\frac{0.2 \text{ mg/kg} \times 100}{7} = 2.9 \text{ mg/kg bw}$$

where

0.2 mg/kg = toxic dose for kidney damage
100/7 = conversion factor for determining oral dose from i.p. dose

At the calculated dose of 2.9 mg/kg bw, one may expect some necrosis of the GI tract as well as fatalities. In fact, LD_{50} values across species have been reported as 10-40 mg/kg bw. Therefore, this method of calculation cannot be used for the estimation of 1-day and 10-day HAs for mercury in drinking water.

Since ionic mercury is very corrosive and precipitates proteins, it is mandatory to establish a threshold dose level for this adverse health effect for mercury in drinking water. Furthermore, a systematic study is required to determine a threshold dose of mercury in drinking water for adverse health effects other than corrosiveness.

Lifetime AADI. The studies of both Fitzhugh et al. (1950) and Druet et al. (1978) can be used for quantification of noncarcinogenic effects of mercury salts. The advantages of the Fitzhugh et al. (1950) study included long duration and the use of the oral route exposure. Disadvantages included use of mercuric acetate and phenylmercuric acetate as test compounds, a small number of animals per group, and relatively insensitive endpoints. Interpretation was also made more difficult by the apparent differing sensitivities of male and female rats.

In the Druet et al. (1978) study, the duration of exposure was only 8-12 weeks; s.c. injection was used instead of oral exposure. However, inorganic mercury salts, the primary form expected to be found in drinking water, were used in this study. The primary endpoints evaluated, antibody formation and proteinurea were more sensitive than those used in the Fitzhugh et al. (1950) study. To increase sensitivity further, a genetically susceptible strain of rats, the Brown Norway, was exposed. The development of a criterion from a study in which a susceptible strain was used is considered justified since reports by Kazantzis et al. (1962) and Tubbs et al. (1982) suggested the presence of similarly increased sensitivities in some humans industrially exposed to mercury compounds.

Based upon the above factors the Druet et al. (1978) study was considered most appropriate for the development of an AADI of mercury in drinking water for humans. In this study the development of kidney disease was evaluated. In the first phase the rats developed anti-GBM antibodies. During the second phase, which is seen after 2-3 months, the patterns of fixation of antisera changed from linear to granular as the disease progressed. The immune response was accompanied by proteinurea and in some cases by a nephrotic syndrome.

Both male and female Brown Norway rats 7-9 weeks of age were divided into groups of 6-20 animals each. The numbers of each sex were not stated. The animals were injected s.c. with mercuric chloride 3 times weekly, for 8 weeks, with doses of 0, 100, 250, 500, 1000 and 2000 µg/kg bw. An additional group was injected with a 50 µg/kg dose for 12 weeks. Antibody formation was measured by the use of kidney cryostat sections stained with a fluorescinated sheep anti-rat IgG antiserum. Urinary protein was assessed by the biuret method.

Tubular lesions were seen at the higher dose levels. Proteinurea was seen at doses of 100 µg/kg and above, but not at 50 µg/kg. Proteinurea was considered a highly deleterious effect in that affected animals developed hypoalbuminemia and many died. Fixation of IgG antiserum was detected in all groups except controls.

For the development of an AADI the NOAEL of 50 µg/kg was selected since antibody formation was not considered to be an adverse effect. Adjustment was made in the calculations to account for the likelihood that absorption efficiency will be greater by the s.c. route; 100% absorption was assumed by the s.c. route and to the extent of 10% by ingestion in humans (absorption estimates of 7-15% cited in the literature -- Rahola et al., 1971; Task Group on Metal Accumulation, 1973). In the 50 µg/kg exposure group a total of 36 doses totaling 1800 µg/kg were injected over the 84-day period of exposure. A factor of 0.739, to adjust for the percentage by weight of mercury in mercuric chloride, was included in the development of the AADI. A safety factor of 1000 was considered appropriate for the extrapolation from a short-term study to a chronic one, for extrapolation from animals to humans, for accounting for the sensitive human and because proteinurea, which is life-threatening, occurred at concentrations of mercury only twice the NOAEL. A body weight of 70 kg and a water intake of 2 ℓ/day are assumed. The AADI is then calculated as follows:

$$\frac{100 \times 1800\ \mu g/kg \times 0.739 \times 70\ kg}{10 \times 84\ days \times 1000 \times 2\ \ell/day} = 5.5\ \mu g/\ell$$

where

1800 μg/kg = calculated total dose

0.739 = a factor to convert mercuric chloride to mercuric ion

70 kg = assumed average weight for a healthy adult

84 days = exposure period

1000 = uncertainty factor

2 ℓ/day = average consumption of drinking water per individual

100/10 = accommodation for absorption factor

This AADI is equivalent to an ADI of ~11 μg/day or ~0.16 μg/kg bw/day. This AADI is also very close to 10 μg/ℓ, which can be determined as the ambient water quality criterion for total mercury (including methyl mercury) (U.S. EPA, 1980). This criterion is derived from a LOEL of 200 μg/day estimated by WHO (1976) for a 70 kg person and divided by an additional 10-fold uncertainty factor. Only an exposure consumption of 2 ℓ water/day was considered. This AADI is not, however, a criterion in that it does not take into consideration other routes of exposure. This latter calculation indicates that the recommended AADI of 5.5 μg/ℓ should be also protective of the effects of methyl mercury on human health.

Carcinogenic Effects

Adequate data regarding carcinogenic effects of mercury could not be located in the available literature.

Quantification of Carcinogenic Effects

Since no definitive carcinogenic effects have been detected, no quantification of effects was attempted.

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